Chapter IV: Rheumatology: Clinical Case Definitions/Diagnoses and Clinical Associations

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Chapter 4: Rheumatology: Clinical Case Definitions/Diagnoses and Clinical Associations

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Rheumatology: Clinical Case Definitions/Diagnoses and Clinical Associations

1. Introduction

The charge from the court to the Panel is to assess whether existing studies, research and reported observations provide a reasonable scientific basis for one to conclude that silicone breast implants cause or exacerbate "classic" connective tissue diseases, atypical presentations, symptoms or immune system dysfunctions.

The following Scope was specified in Order No 31E:

- Classic connective tissue disease such as systemic lupus erythematosus, Sjögren's syndrome etc.
- Atypical presentations of connective tissue diseases.
- Symptoms (a listing of symptoms and signs was appended)
- Immune system dysfunctions (this category of immune system dysfunction is not addressed here since it is reviewed in detail in the Immunology Chapter).

The categories specified in Order No 31E (classic connective tissue disease, atypical presentations, symptoms and signs), require case-definitions that can be used for clinical diagnosis. Clinical diagnosis is the crucial process that labels patients and classifies their diseases (Sackett, 1991). The word "disease" is an ambiguous term but in this context it can usefully be conceptualized as an agreed upon case definition of a "target disorder" that is the objective of the diagnostic process. Target disorders consist of clusters of symptoms (manifestations of the target disorder that the subjects themselves perceive either spontaneously or on questioning), signs (manifestations perceived by their clinicians during an examination) and laboratory/radiological findings (results that reflect maladaptive alterations in structure or function). The above approach is consistent with that described by Dr. Robert Willkens in his September 10th 1996 submission to Judge Robert E. Jones (Wilkens, 1996) in which he states: "The scientific methodology of arriving at a hypothesis by observation, in the matter of symptoms in patients who have previously undergone silicone breast implantation would seem appropriate and incontestable. A clinician considers the history of the development of symptoms, performs a physical examination, obtains laboratory studies such a x-rays, electrocardiograms and additional studies in establishing a diagnosis. But in arriving at a specific diagnosis he must consider all those conditions which might

present with some or all of the findings and finally the diagnostician selects the diagnosis which best fits the findings on the basis of common knowledge. This process in called differential diagnosis. Cardinal elements of arriving at a correct diagnosis are objective determinations in any of the facets of the examination. (Degown and Degown, 1969). In arriving at a diagnosis the physician is encouraged to employ the principle called the Law of Parsimony that encourages the choice of a single disease to explain the patient's disease manifestations. This "law" must be applied cautiously since the experienced clinician recognizes the likelihood of multiple disorders contributing to the patient's symptoms. The clinician must then differentiate, if he can, the patient's symptoms as unique to a disease which he designates as being present."

The Findings of Fact Documents, and the supporting material submitted by both legal parties provided an excellent review of the clinical studies themselves, their strengths and weaknesses. There is no dispute that there is sound documentation of the presence of a wide variety of connective tissue/autoimmune diseases and symptoms in women with silicone breast implants. However, this does not automatically lead to the conclusion that silicone breast implants are the cause of the clinical conditions. In such a large number of women with implants all of these conditions will occur independently in this population. To support the hypothesis that silicone breast implants are causing additional cases of connective tissue/autoimmune diseases, it is necessary to demonstrate an increased incidence of these conditions in women with silicone breast implants, compared to women without such implants. This is best assessed through estimating the strength of the association. Although the case series and case reports are critical to establishing a clinical case definition, assessing the strength of association requires studies with appropriate control groups using cohort, case-control, or cross-sectional designs (see also Epidemiology Chapter).

The remainder of this chapter is structured to review each category (Classic/Accepted Diagnosis, Atypical Presentations of Connective Tissue Disease, Symptoms and Signs) first for the Clinical Case Definition/Diagnosis and then for a review of the Strength of Association.

The categories of systemic disease specified in Order no 31E will now be reviewed.

II. Classic/Accepted Connective Tissue Diseases, Such As Systemic Lupus Erythematosus, Sjögren's Syndrome Etc.

Clinical Case Definition/Diagnosis

We have interpreted the word 'classic' to include established connective tissue/autoimmune diseases that are described in the major textbooks and accepted by the majority of the rheumatology medical community. We have added the term autoimmune to include diseases such as Hashimoto's Thyroiditis, Multiple Sclerosis and Myasthenia Gravis which are included in the submissions submitted by legal counsel.

Established/Classic Connective Tissue/Autoimmune Diseases include:

Ankylosing Spondylitis; Arthritis Associated with Inflammatory Bowel Disease; Chronic Fatigue Syndrome; Dermatomyositis Polymyositis; Fibromyalgia; Hashimoto's Thyroiditis; Localized or Discoid Lupus; Mixed Connective Tissue Disease; Morphea Multiple Sclerosis; Myasthenia Gravis; Polyarteritis Nodosa; Polychondritis; Polymyalgia Rheumatica; Psoriatic Arthritis; Raynaud's Disease/Phenomenon; Rheumatoid Arthritis Sarcoidosis; Scleroderma; Sjögren's Syndrome; Systemic Lupus Erythematosus; Temporal Arteritis; Vasculitis; Wegener's Granulomatosis.

Explicit criteria have been established for a number of these (i.e. Dermatomyositis/Polymyositis; Fibromyalgia; Rheumatoid Arthritis; Scleroderma; Sjögren's Syndrome; Systemic Lupus Erythematosus) (The Arthritis Foundation, 1997). The standard textbooks describe in a reasonably consistent fashion, the case definition for each cluster, or constellation of the symptoms, signs and diagnostic test results.

Strength of Association

Methodology

The basic methodology for assessing the Strength of Association is described here for all three categories (Classic/Accepted, Atypical Presentations and Symptoms and Signs).

1) Literature Search

Three methods were used to identify potentially relevant studies: 1) screening of all legal submissions supplied by the Kobayashi legal firm; 2) a search of computerized bibliographical databases; and 3) a review of references cited in the retrieved articles.

For the computerized search, four search strategies designed to focus on different subsets of rheumatological/autoimmune disease, were run on five bibliographic databases. MEDLINE (1966-

September 1998), Current Contents (January 1997 - week 13 1998), HealthSTAR (1990 - December 1996), and Biological Abstracts (1990 - September 1996) were searched using OVID version 3.0. EMBASE (1980- April 1997) was searched using Silver Platter's WinSPIRS version 2.0. The search strategies were initially developed for MEDLINE and then modified to search the indices of the other databases. In an attempt to retrieve any studies pertaining to atypical presentations, symptoms or neurological disorders that may have been missed, MEDLINE (1996-September 1998), Toxline (1965-Sept 1998) via Internet Grateful Med. and Dissertation Abstracts (1997-1998) from Dissertation Services at: http://www.umi.com were searched with a fifth strategy to capture these less uniform terms. (See Appendix A for details).

2) Study Selection

The panel received over 3600 documents from the legal councils of the parties. One thousand six hundred articles were identified through the computerized searches. Some were duplicates.

The titles of all legal submissions were screened independently by two reviewers. Each citation was categorized as: potentially relevant, insufficient information to make a judgment, or ineligible. All citations classified, by one or both of the reviewers, as potentially relevant or as insufficient information to make a judgment were retrieved and classified as eligible or ineligible according to predetermined inclusion criteria. All ineligible citations were coded according to the reason for exclusion. Disagreements were resolved through discussion and consensus. A final list of included citations from the legal submissions was generated.

The titles and abstracts of computerized database search printouts were screened independently by two reviewers, and categorized as eligible or ineligible according to the same predetermined criteria. Disagreements were resolved through discussion and consensus. A final list of included citations from the database search was generated.

A priori selection criteria were:

a) human studies;

b) total number of participants equal to or greater than ten;

c) appropriate control group of either healthy or unexposed women, fulfilling the requirements of the study design (i.e. cohort, case-control, or cross-sectional studies);

d) for multiple publications of the same data, only one publication using the same data was included in the review;

e) no language restrictions were imposed;

f) no restrictions were imposed on publication dates for the legal submissions and computerized database searches were limited to 1962-1998.

3) Data Extraction

A standard form (see appendix B) was used to collect information from the selected manuscripts, regarding study design, population characteristics, exposure to implants (type, duration, complications, explantation, outcome measure (self-report and/or diagnostic criteria) and results. In particular, the types of breast implants included silicone gel-filled, saline-filled or polyurethane-coated. Information was extracted independently by two reviewers. Discrepancies in data extraction were discussed and resolved through consensus.

4) Data Synthesis

The magnitude of the association between breast implants (exposure) and a connective tissue disease under consideration (outcome) is expressed as a relative risk (RR) or an odds ratio (OR). The RR is obtained directly from a cohort study and the OR from case-control and cross-sectional studies. If the estimates were corrected for the effects of confounding factors they are called adjusted estimates, otherwise unadjusted. In addition to the point estimate, the 95% confidence interval (CI) estimate are used, which defines a range within which the true value for the association between exposure and outcome is most likely to be found. If the study provided adjusted RRs or ORs, they were reported, otherwise unadjusted RRs and ORs were calculated and reported. These calculated risk estimates and confidence intervals should be interpreted with caution, since in many instances the number of cases reported are small and approximate methods need to be used.

A RR or OR of 1.0 indicates no observed association between exposure and outcome; a number appreciably larger than 1.0 indicates a likely increase in risk associated with the exposure, whereas a number appreciably smaller than 1.0 indicates a likely risk reduction. As indicated in the Epidemiology

Chapter, the decision that a value is 'appreciably' larger than 1.0 is generally based on whether the lower boundary of the 95% confidence interval exceeds 1.0 for increased risks or the upper boundary is less than 1.0 for decreased risks.

For meta-analysis of adjusted effects, approximate large-sample statistical methods were used. These methods are outlined in Appendix B, Section B.1 of the Epidemiology Chapter.

Study Results Reported For Accepted Diagnoses

Twenty studies using cohort, case-control or cross-sectional designs were identified, namely: (Burns, 1996; Dugowson, 1992; Edworthy, 1998; Englert, 1996; Friis, 1997; Gabriel, 1994; Goldman, 1995; Hennekens, 1996; Hochberg, 1996; Lacy, 1997; Macdonald, 1996; Nyren,1998a; Nyren, 1998b; Park, 1998; Sanchez-Guerrero, 1995; Strom,1994; Teel 1997; Wells, 1994; Winther, 1998; Wolfe,1995). Details regarding these studies may be found in Table 1.

Although some individual studies show some degree of elevation of risk, as given by the relative risk or odds ratio, these are not substantial or consistent for any of these conditions. For the studies reported here, no risk estimate has a lower confidence interval greater than one.

The details, analysis and results for the following diagnoses are given in the Epidemiology Chapter.

Dermatomyositis/Polymyositis-see Epidemiology Chapter for details

Friis 1997
Goldman 1995
Hennekens 1996
Nyren 1998a
Sanchez-Guerrero 1995
Teel 1997

Rheumatoid Arthritis-see Epidemiology Chapter for details

Dugowson 1992
Edworthy 1998
Friis 1997
Gabriel 1994
Goldman 1995
Hennekens 1996
Nyren 1998
Park 1998

Sanchez-Guerrero 1995
Wolfe 1995

Scleroderma-see Epidemiology Chapter for details

Burns 1996
Edworthy 1998
Englert 1996
Friis 1997
Gabriel 1994
Goldman 1995
Hennekens 1996
Hochberg 1996
Lacey 1997
Nyren 1998
Sanchez-Guerrero 1995
Wells 1994

Sjögren's Syndrome - see Epidemiology chapter three for details

Edworthy 1998
Friis 1997
Gabriel 1994
Goldman 1995
Hennekens 1996
Nyren 1998a
Sanchez-Guerrero 1995

Systemic Lupus Erythematosus - see Epidemiology Chapter for details

Edworthy 1998
Friis 1997
Goldman 1995
Hennekens 1996
Nyren 1998a
Sanchez-Guerrero 1995
Strom 1994
Wells 1994

Diagnoses not discussed in the Epidemiology chapter are divided into and discussed in the following categories:

1) Diagnoses for which there are no data reported;

2) Diagnoses for which there is no study reporting an estimate with a lower confidence limit of greater than one (or the limit could not be calculated with information provided);
3) Diagnoses for which there are discordant results (i.e. at least one but not all studies report an estimate with a lower confidence limit of greater than one); and
4) Diagnoses for which there are concordant results (i.e. all studies report an estimate with a lower confidence limit of greater than one).

1) Diagnoses for which there are no data reported

Morphea

2) Diagnoses for which there is no study reporting an estimate with a lower confidence limit of greater than one

Ankylosing Spondylitis

Friis 1997 Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 0 cases in 2570 exposed (0.0%); unexposed not reported
Relative Risk: na

Gabriel 1994 Design: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year
Frequencies: 0 cases in 749 exposed (0.0%); 3 cases in 1498 unexposed (0.26%)
Relative Risk (adjusted/calculated): 0.29 (0.01, 5.52)

Nyren 1998a Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 1 case in 7442 exposed (0.01%); 0 cases in 3353 unexposed (0.0%)
Relative Risk (unadjusted/calculated): 1.35 (0.06, 33.18)

Arthritis Associated with Inflammatory Bowel Disease

Gabriel 1994 Design: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year
Frequencies: 1 case in 749 exposed (0.13%); 0 cases in 498 unexposed (0.0%)
Relative Risk (adjusted/calculated): 2.00 (0.08, 48.90)

Chronic Fatigue Syndrome

Macdonald 1996
Design: Case-Control
Implant Type: any
Factors Controlled: Design - neighbourhood, age
Frequencies: 1 exposure in 35 cases (2.86%); 2 exposures in 35 controls (5.71%)
Odds Ratio (adjusted/calculated): 0.49 (0.01,9.84)

Fibromyalgia

Nyren 1998a
Design: Cohort
Implant Type: any
Factors Controlled: Analysis - age, length of follow up
Frequencies: 9 cases in 7442 exposed (0.12%); 5 cases in 3353 unexposed (0.15%)
Relative Risk (adjusted/article): 1.0 (0.3, 3.0)

Wolfe 1995
Design: Case-Control
Implant Type: silicone breast implants
Factors Controlled: Analysis - age
Frequencies: 4 exposures in 533 cases (0.57%); 4 exposures in 1134 controls (0.35%)
Relative Risk (adjusted/article): 2.11 (0.51, 8.77)

Hashimoto's Thyroiditis

Friis 1997
Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 0 cases in 2570 exposed (0.0%); unexposed not reported
Relative Risk: na

Gabriel 1994
Design: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year; Analysis - age, index year
Frequencies: 10 cases in 749 exposed (1.34%); 21 cases in 1498 unexposed (1.40%)
Relative Risk (adjusted/article): 1.00 (0.47, 2.13)

Localized or Discoid Lupus

Friis 1997
Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 0 cases in 2570 exposed (0.0%); unexposed not reported
Relative Risk: na

Nyren 1998a
Design: Cohort:
Implant Type: any

Factors Controlled: none
Frequencies: 1 case in 7442 exposed (0.01%); 0 cases in 3353 unexposed (0.0%)
Relative Risk (unadjusted/calculated): 1.35 (0.06, 33.18)

Mixed Connective Tissue Disease

Goldman 1995
Design: Cross-Sectional
Implant Type: any
Factors Controlled: Analysis-age at first visit, income
Frequencies: 0 cases in 150 exposed (0.0%); 49 cases in 4097 unexposed (1.20%)
Odds Ratio (unadjusted/article): 0.00 (0.00, 2.68)

Sanchez-Guerrero 1995
Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 0 cases in 1183 exposed (0.0%); 0 cases in 86,318 unexposed (0.0%)
Relative Risk (unadjusted/calculated): 17.55 (0.35, 884.24)

Teel 1997
Design: Case-Control
Implant Type: any
Factors Controlled: none
Frequencies: 0 exposed in 3 cases (0.0%); 40 unexposed in 3249 controls
Odds Ratio (unadjusted/calculated): 11.32 (0.58, 222.74)

Multiple Sclerosis

Nyren 1998b
Design: Cohort
Implant type: any
Factors Controlled: Analysis - age, follow-up
Frequencies: 3 cases in 7429 exposed (0.04%); 4 cases in 3351 unexposed (0.12%)
Relative Risk (adjusted/article): 0.5 (0.2, 0.9)

Winther 1998
Design: Cohort
Implant type: unspecified
Factors Controlled: none
Frequencies: 2 cases in 1135 exposed (0.18%); 2 cases in 7071 unexposed (0.03%)
Relative Risk (unadjusted/calculated): 6.23 (0.88, 44.18)

Myasthenia Gravis

Winther 1998
Design: Cohort
Implant type: unspecified
Factors Controlled: none
Frequencies: 0 cases in 1135 exposed (0.0%); 1 case in 7071 unexposed (0.01%)

Relative Risk (unadjusted/calculated): 2.08 (0.08, 50.91)

Polyarteritis Nodosa

Friis 1997
Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 0 cases in 2570 exposed (0.0%); unexposed not reported
Relative Risk: na

Nyren 1998a
Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 0 cases in 7442 exposed (0.0%); 0 cases in 3353 unexposed (0.0%)
Relative Risk (unadjusted/calculated): 0.45 (0.01, 22.71)

Polychondritis

Gabriel 1994
Design: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year
Frequencies: 1 case in 749 exposed (0.13%); 0 cases in 1498 unexposed (0.0%)
Relative Risk (adjusted/calculated): 6.00 (0.24, 147.01)

Polymyalgia Rheumatica

Gabriel 1994
Design: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year
Frequencies: 2 cases in 749 exposed (0.27%); 1 case in 1498 unexposed (0.07%)
Relative Risk (adjusted/calculated): 4.00 (0.36, 44.04)

Friis 1997
(combined with Temporal Arteritis)
Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 3 cases in 2570 exposed (11.7%); 10 cases in 11023 unexposed (0.09%)
Relative Risk (unadjusted/calculated): 1.29 (0.35, 4.67)

Psoriatic Arthritis

Friis 1997
Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 0 cases in 2570 exposed (0.0%); unexposed not reported
Relative Risk: na

Gabriel 1994 Design: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year
Frequencies: 0 cases in 749 exposed (0.0%); 1 case in 1498 unexposed (0.07%)
Relative Risk (adjusted/calculated): 0.67 (0.03, 16.33)

Nyren 1998a Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 0 cases in 7442 exposed (0.0%); 2 cases in 3353 unexposed (0.06%)
Relative Risk (unadjusted/calculated): 0.09 (0.00, 1.88)

Raynaud's Disease/Phenomenon

Giltay 1994 Design: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - age, year of operation
Frequencies: 12 cases in 325 exposed (3.69%); 7 cases in 210 unexposed (3.33%)
Relative Risk (adjusted/calculated): 1.11(0.44, 2.77)

Park 1994 Design: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - Augmentation - "similar aged"; Reconstruction - partially matched on age, stage of disease and time of operation
Frequencies:
Augmentation: 1 case in 110 exposed (0.91%); 3 cases in 128 unexposed (2.34%)
Reconstruction: 7 cases in 207 exposed (3.38%);5 cases in 88 unexposed (5.68%)
Relative Risk (adjusted/calculated):
Augmentation: 0.39 (0.04, 3.68);
Reconstruction: 0.60 (0.19, 1.82)

Wells 1994 Design: Cohort
Implant Type: silicone breast implants
Factors Controlled: none
Frequencies: 1% cases in exposed group; 0% cases in unexposed group
Relative Risk: na

Sarcoidosis

Friis 1997 Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 0 cases in 2570 exposed (0.0%); unexposed not reported
Relative Risk: na

Nyren 1998a Design: Cohort

Implant Type: any
Factors Controlled: none
Frequencies: 2 cases in 7442 exposed (0.03%); 2 cases in 3353 unexposed (0.06%)
Relative Risk (unadjusted/calculated): 0.45 (0.06,3.20)

Temporal Arteritis

Friis 1997 (combined with Polymyalgia Rheumatica)
Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 3 cases in 2570 exposed (0.12%); 10 cases in 11023 unexposed (0.09%)
Relative Risk (unadjusted/calculated): 1.29 (0.35, 4.67)

Nyren 1998a
Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 1 case in 7442 exposed (0.01%); 0 cases in 3353 unexposed (0.0%)
Relative Risk (unadjusted/calculated): 1.35 (0.06, 33.18)

Vasculitis

Gabriel 1994
Design: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year
Frequencies: 0 cases in 749 exposed (0.0%); 2 cases in 1498 unexposed (0.13%)
Relative Risk (adjusted/calculated): 0.40 (0.02, 8.32)

Wegener's Granulomatosis

Friis 1997
Design: Cohort
Implant Type: any
Factors Controlled: none
Frequencies: 0 cases in 2570 exposed (0.0%); 0 cases in 11023 unexposed (0.0%)
Relative Risk (unadjusted/calculated): 4.29 (0.09, 216.04)

A meta-analysis was possible for four diagnoses, and the results, as given by the pooled relative risk and confidence interval, are as follows:

Multiple Sclerosis	Relative Risk (95 % Confidence Interval)
(including unadjusted estimates)	
Nyren 1998b	0.5 (0.2, 0.9)
Winther 1998	6.23 (0.88, 44.18)
Overall	0.69 (0.34, 1.40)
Raynaud's Disease/Phenomenon	
Giltay 1994	1.11 (0.44, 2.77)
Park 1994 Augmentation	0.39 (0.04, 3.68)
Overall	0.96 (0.41, 2.25)
Fibromyalgia	
Nyren 1998	1.0 (0.3,3.0)
Wolfe 1995	2.11 (0.51, 8.77)
Overall	1.34 (0.55, 3.29)
Polymyalgia Rheumatica	
(including unadjusted estimates)	
Gabriel 1994	4.00 (0.36, 44.04)
Fries 1997	1.29 (0.35, 4.67)
Overall	1.66 (0.53, 5.21)

3) Diagnoses for which there are discordant results (i.e. at least one but not all studies report an estimate with a lower confidence limit of greater than one)

None

4) Diagnoses for which there are concordant results (i.e. all studies report an estimate with a lower confidence limit of greater than one)

None

This data does not provide any evidence for an association between silicone breast implants and these Classic/Accepted connective tissue diseases.

III. Atypical Presentations of Connective Tissue Diseases: Undifferentiated Connective Tissue Disease (UCTD)

Two constellations of symptoms, signs and laboratory test abnormalities have been proposed that are not in the majority of textbooks, namely Undifferentiated Connective Tissue Disease and Systemic Silicone Related Disease.

Clinical Case Definition/Diagnosis

In order to be able to study such atypical presentations there needs to be an accepted case definition that has been shown to differ from other conditions in its constituent clinical presentation, impact upon prognosis, severity or response to therapy.

Undifferentiated connective tissue disease provides a good example of how a case definition is established and the natural history assessed. The term has been used since the early 1980s (Leroy, 1980; Rich, 1984; Strongwater, 1989) to describe patients who do not meet the criteria for other accepted connective tissue diseases, but who have a constellation of the symptoms that are found in the accepted connective tissue diseases.

An important study (Williams, 1998) has been conducted to standardize the case definition, and to follow a cohort of 410 patients with well defined and undifferentiated connective tissue diseases over 5 years to assess the natural history and outcome. The case definition was defined by a group of experienced rheumatologists under the auspices of the Coordinating Center of the Cooperative Systemic Studies of the Rheumatic Diseases, funded under the National Institute of Arthritis, Musculoskeletal and Skin Diseases. A protocol was developed at the Coordinating Center with the assistance and approval of participating clinics and under the direction and guidance of an external advisory committee. Early Undifferentiated Connective Tissue Disease was defined as patients with disease manifestations of less than one year in duration that met at least one of the following criteria: 1) Raynaud's phenomenon; 2) isolated keratoconjunctivitis SICCA; 3) unexplained polyarthritis (including possible and probable rheumatoid arthritis); or 4) at

least three other criteria that could not be attributed to other disease processes, which included myalgias, rash, pleuritis, pericarditis, central nervous system symptoms, pulmonary symptoms, peripheral neuropathy, elevated erythrocyte rate, and a false positive serologic test for syphilis.

The above group of investigators followed 115 undifferentiated patients over five years. Thirty four patients were lost to follow-up. Of the remaining 81 patients, the five year actuarial survival was 94%, similar to patients with rheumatoid arthritis, systemic lupus erythematosus or dermatomyositis/polymyositis. Ten patients experienced complete remission, 34 patients persisted with undifferentiated disease, 18 patients went on to fulfill the diagnostic or classification criteria for a specific disease. The response to therapy of patients with UCTD is not well documented with the exception of one study by Wise (1996) in which patients with UCTD (defined as having two to three criteria for Systemic Lupus Erythematosus (SLE)), respond as well to methotrexate, as do those who meet the full criteria for SLE.

The Panel is comfortable with including UCTD as a constellation given that it has a case definition, is distinct from the other established connective tissue diseases, has been studied longitudinally, and has substantive symptoms, which in many patients have been shown to be stable over time. In addition, the criteria do not require the presence of silicone gel. This allows studies to be conducted to assess its putative association with silicone gel (Liang, 1996).

Strength of Association

Methodology

The same methods were applied as for the Classic/Accepted diseases and the results are shown below.

Study Results Reported For Atypical Presentations: UCTD

UCTD was included explicitly in one case control study (Liang, 1996) and although not analyzed separately would possibly apply to a number of the patients included in cross sectional or cohort studies. (Edworthy, 1998; Friis, 1997; Gabriel,1994; Giltay,1994; Hennekens, 1996; Nyren,1998; Park,1998; Wells,1994)

The study addressing this outcome had an estimate with lower confidence interval greater

than one indicating no appreciably increased risk.

Liang 1996 Design: Case Control
Implant Type: unspecified
Factors Controlled: Design - age, race, geographic location:
Analysis - year of birth
Frequencies: 3 exposures in 205 cases (1.46%); 27 exposures in 2220 controls (1.21%)
Odds Ratio (adjusted/article): 2.27 (0.67, 7.71)

This study was only available as an abstract. The study found only 3 cases out of 205 women with implants. The confidence limits for the adjusted odds ratio are very wide with the lower bound of 0.67, well below the criteria level of 1.0 for defining an appreciable association. This is insufficient to substantiate an association with silicone breast implants.

IV. Atypical Presentation of Connective Tissue Diseases: Proposed Systemic Silicone Related Disease (SSRD)

Clinical Case Definitions

The second constellation of atypical presentation of connective tissue diseases for which a case definition has been proposed, that is not in the majority of textbooks, is that of the proposed Systemic Silicone Related Disease.

The history of SSRD being proposed as a disease is well summarized in the Findings of Fact from the plaintiffs. In the early 1990s, rheumatologists were reporting an increasing number of case series of women with implants with a wide variety of rheumatological symptoms. It was noted that many of these women did not have classical connective tissue disease and it was suggested that perhaps they were experiencing an atypical disease (Bridges, 1993; Love, 1992).

Weiner et al, (1992) reported on 50 patients with Silicone Breast Implants (SBIs) all of whom had arthralgias, and many of whom had myalgias, neuralgias, recurrent flu-like sensations and profound fatigue. Sixty percent reported dry eyes/mouth and Anti-nuclear Antibodies (ANAs) were positive in 70% of women. None met ACR criteria, and none responded to traditional therapy.

Osborn (1992) described symptoms of breast pain and hardening, fatigue, weakness, muscle aches, widespread pain, and breast lumps in 50% of 100 women with Silicone Breast Implants. Less than 20% met American College of Rheumatology (ACR) criteria for classical Connective Tissue

Disease (CTD). Subsequently, Osborn and colleagues (1993) reported a series of 126 women with rheumatological complaints, none of whom fulfilled ACR criteria for classical Connective Tissue Disease.

Vasey (1994) reported the clinical findings of 50 Silicone Breast Implant patients between 1977 and 1991. The most common clinical findings included chronic fatigue, muscle pain, joint pain, joint swelling and lymphadenopathy. Twenty percent were judged to have classical connective tissue disease.

By 1995, the reports of atypical connective tissue disease were growing and the literature contained an increasing number of case series. Freundlich (1994) reviewed 50 consecutive women with Silicone Breast Implant and found 50% had complaints of dry eyes and dry mouth. The same year, Borenstein described symptoms of fatigue, myalgias and arthralgias reported by a proportion of 100 patients, who on average reported the onset of clinical symptoms 5.6 years after mammoplasty. In 1995, Davis reported on 343 patients with arthralgias (71%), chronic fatigue (85%), dry eyes (69%) and numbness (69%). Mease and colleagues (1995) reported a series of 128 symptomatic women with Silicone Breast Implants. The average interval between implantation and onset of symptoms was 5.8 years. The authors concluded that their results suggested the presence of a syndrome marked by fatigue, polyarthralgias, myalgias, cognitive dysfunction, SICCA syndrome, rash, chest wall pain, sleep and mood disturbance and occasional serologic abnormalities. Baker reported on 145 patients with Silicone Breast Implant who reported symptoms of Sjögren's syndrome, alopecia, arthralgia and skin rashes which seemed to represent a clustering that is different from fibromyalgia or primary generalized osteoarthritis. Cuellar (1995) reported on 813 patients with Silicone Breast Implants, many with an ill-defined connective tissue diseases. Predominant complaints were malaise, fatigue, lymphadenopathy, arthralgia and myalgia.

Solomon reported similar findings in 1994 on his first 176 patients. By 1996 he reported on a patient base of 639 symptomatic women. The mean implant duration was 12.4 years. Four hundred and fifty six of the women had a history of Baker Grade IV contracture and 216 had documented implant rupture. The most frequently reported symptoms were fatigue, cognitive dysfunction, arthralgias, and dry mouth. Three hundred and thirty two of the patients had their implants removed. Of these, 215 were followed for six months following explantation with clinical improvement seen in 36%. Solomon (1994) concluded that these women had a unique disease which tends to occur in women with long-standing implants who have antecedent pathology in the form of capsular contracture

and implant rupture.

The Executive Committee of the Silicone Related Disorders Research Group (1996) have proposed the following set of preliminary operational criteria for a syndrome/disease that they term Systemic Silicone Related Disease.

Inclusion Criteria:

A. Presence of a silicone gel filled breast implant either currently or in the past

B. Presence of local disease: Any of the following
1. Capsular contracture (Baker ll or greater)
2. Rupture documented by imaging technique (sonogram or MRI), operative findings, or presence of siliconoma
3. Persistent (more than 6 weeks) chest wall pain
4. Persistent (more than 6 weeks) breast pain unrelated to menses
5. Axillary adenopathy
6. Entrapment neuropathy or thoracic outlet syndrome documented by physical exam (positive Adson's sign) or by electrodiagnostic studies
7. Immune mediated skin rash (petechiae, telangiectasia, or poikiloderma not related to sun exposure) on the chest wall
8. Histopathologic finding in capsule of immune granuloma (foamy macrophages, plasma cells, or lymphoid infiltrates)

To be considered definite SSRD, both A and B must be present unless the implant is polyurethane coated in which case only A must be present.

Exclusion Criteria:

A. Presence of classic connective tissue disease
1. Rheumatoid Arthritis by ACR criteria
2. Systemic Lupus Erythematosis by ACR criteria
3. Primary Systemic Sclerosis (PSS) by ACR criteria or biopsy
4. Mixed Connective Tissue Disease with positive anti-RNP antibody
5. Dermatomyositis/Polymyositis by Bohan criteria
6. Primary Sjögren's Syndrome by Fox Criteria

B. Presence of local or metastatic malignancy excluding skin cancer or carcinoma in situ.

C. Exposure to another environmental agent or drug know to produce systemic rheumatic disease

D. Documented chronic and persistently active infection prior to implantation. Does not exclude

patients with positive serologies for past viral or bacterial infection who lack evidence of active infection at time of implantation.

Major Criteria:

(Defined as those signs or symptoms present in 50% or more women in 2 or more published series). The symptom must be either objectively verifiable or sufficiently severe to interfere with activities of daily living, vocational activities, and/or recreational activities.

A. Symmetrical myalgia with 4-11 tender points, including four or more tender points above the waist. Ascertainment of tender points includes appropriate negative control points.

B. Chronic fatigue of six month duration or longer interfering with activities of daily living or occupational and/or recreational activities.

C. Cognitive dysfunction of six month duration or longer which can either be objectively demonstrated on neuropsychiatric testing or which is of sufficient severity to interfere with activities of daily living and occupational and/or recreational activities.

D. Objective SICCA complex defined by abnormal Schirmer testing, abnormal Rose Bongal staining, salivary scintography, sialogram or abnormal labial biopsy.

Minor Criteria:

(Defined as those signs, symptoms or laboratory findings seen in 50% or more symptomatic women in two or more published series without objective confirmation or in 25-50% of symptomatic women with objective confirmation).

A. Local disease (see above) after onset of systemic disease. (This criteria may only be applied to patients with polyurethane implants who did not satisfy inclusionary criteria B)

B. Arthralgia (pain lasting for six months or longer in four or more upper extremity joints which do not have radiographic evidence of osteoarthritis).

C. Enthesopathy in 2 or more sites in the upper extremities

D. Subjective SICCA complex (2 of 3: dry eye, dry mouth, dry vagina)

E. Cerebello-vestibular dysfunction demonstrated on physical examination or by electrophysiologic testing.

F. Non-scarring alopecia not attributable to pregnancy

G. Raynaud's phenomenon with observed 2 or 3 color change

H. Photosensitive skin rash

I. Immune mediated skin rash (petechiae, telangiectasia, or livedo reticularis) involving both the trunk and extremities)

J. Improvement of two Major or one Major and four Minor criteria within 18 months of explantation

K. Positive ANA at a titer of 1:40 or greater on a Hep-2 cell line

L. Elevated ESR (Westergren>25)

M. Abnormal quantitative immunoglobulins (one or more isotypes)

Definite SSRD requires:

1) Presence of the inclusion criterion

2) Absence of the exclusion criterion

3) Presence of three major criteria, or presence of two major criteria and four minor criteria, or presence of one major and seven minor criteria.

These criteria were derived from the clinical experience with 639 patients reported by Solomon and the patients that had been seen by other members of the Silicone Related Disorders Study Group, a non-profit clinical research organization. The requirement that there be a history of breast implant is of concern to the Panel, since the requirement of the inclusion of the putative cause of silicone exposure as one of the criteria , does not allow the criteria set to be tested objectively without knowledge of the presence of implants thus incurring 'incorporation bias' (Sackett, 1979).

Another concern of the Panel is that there are few objective signs and that the constellation proposed is not unique. The majority of components of the proposed SSRD criteria are already part of other accepted diseases (e.g. scleroderma, Sjögren's, lupus, fibromyalgia, chronic fatigue syndrome) with the only differentiating feature being that SSRD requires the presence of a breast implant.

A consensus statement was developed following a meeting of a consensus panel of nine practicing rheumatologists with extensive experience with patients having silicone exposure in October 1995. An abstract at the 1996 ACR describes the application of preliminary operational criteria to 100 cases with what is termed atypical connective tissue disease (ACTD), another 60 cases with implants and no systemic complaints, and 37 patients with a diagnosis of fibromyalgia without implants. The authors

state that "the selection of the cases of ACTD were obtained by random or consecutive selection from four university based urban practices." The exact criteria for the selection of these patients are not stated in this abstract. All charts were reviewed by two of the authors and a given patient was considered to have fulfilled these putative criteria for SSRD if the two reviewers found the documentation to meet these criteria. Sensitivity and specificity were calculated. An abstract from the 1996 ISEE Annual Conference provides similar information although some patients with classic connective disease are included. This latter abstract describes the approach but does not include any results. This study does not provide the needed information around patients presenting with none or a more of the exact symptoms proposed to assess whether these are more frequent in those with implants. The patients with implants but no symptoms are by definition not going to contribute to this, and the patients with fibrositis will have been selected out on the basis of their own constellation of signs and symptoms.

The authors have called for a large multicenter disease classification study, but this has not been completed to our knowledge. Such a study will require an evaluation of a representative sample of women with implants (that are not self selected from those with complaints) compared with a matched population group to examine the frequency of the presence of the proposed criteria.

The Panel has carefully considered the above information, as well as presentations at the hearings by Drs. Solomon and Silverman, complemented by Plaintiff Exhibit 434 by Solomon (1996) that presents evidence in support of there being a unique atypical connective tissue disease in women with silicone breast implants.

The Panel has concluded that they do not yet support SSRD being included in the list of accepted diseases for the following reasons:

1. That the requirement of the inclusion of the putative cause (silicone exposure) as one of the criteria does not allow the criteria set to be tested objectively without knowledge of the presence of implants thus incurring incorporation bias.

2. There are few objective signs, and the constellation proposed is not unique. That is a majority of components of the proposed SSRD criteria are already part of other accepted diseases (e.g. scleroderma, Sjögren's, lupus, fibromyalgia, chronic fatigue syndrome) with the only differentiating feature being that SSRD requires the presence of a breast implant.

3. There is no proven association of the criteria set, with the putative cause - exposure to silicone gel and/or silica, through well controlled studies. If a cohort design is used, this requires study of a representative sample of women with implants that are not self selected from those with complaints compared with a matched population group to examine the frequency of such symptoms.

Although this conclusion is subject to revision if the appropriate well designed studies are conducted. The Panel, on balance, concludes that at present the scientific basis is insufficient to accept this as a established disease or syndrome.

V. Symptoms

Clinical Case Definition

The mandate from Judge Pointer in Order 31E states: Listed in the appendix to this order are various diseases, symptoms, conditions or complaints that have sometimes been asserted as possibly associated with silicone gel implants. To the extent you believe appropriate - and without being asked to address separately each of these diseases, symptoms, conditions, and complaints- you are encouraged to comment on the scientific basis, if any, for any such claimed linkage. The Appendix to Order 31E from Judge Pointer lists the following symptoms and signs reported in women exposed to Silicone Breast Implants, but in whom the accepted criteria for any of the above conditions are not met:

> Allergies; Alopecia; Arthralgias; Breathing difficulties/shortness of breath/pulmonary symptoms; Bruising easily; Burning in chest/heartburn/esophageal symptoms; Chronic fatigue/low energy; Chronic inflammation; Cognitive dysfunctions/memory problems; Concentration difficulties; Constipation; Coughing; Diarrhea; Decrease in sex drive; Fever/low grade; Flu-like feelings; Headaches; Heart palpitations; Hot flashes; Incontinence; Infections Lymphadenopathy; Malaise/general; Mood swings/irritability/anxiety/panic attacks; Mucosal ulcers; Muscle cramps; Muscle weakness; Myalgias ; Nausea/vomiting; Neurologic deficits; Night sweats; Pain (abdominal, back, chest, intestinal, joint, muscle); Paraesthesia/numbness and tingling; Sensitivity to heat/cold; SICCA symptoms (dry eyes/mouth/skin/vagina); Skin changes/rashes/hives; Sleep disorders; Sore throat; Stiffness; Swallowing difficulties/dysphagia; Swelling/fluid retention/bloating; Tenderness/tender points; TMJ problems;

Urination/frequency/burning/incontinence; Vertigo/dizziness/ringing in ears/vestibular dysfunction; Vision problems/blurred vision/light sensitivity; Weight loss; Weight gain.

The more than 50 case reports and clinical series describing these in the Findings of Fact of the Plaintiffs were reviewed. The precision of the Case Definition of the symptoms and signs varied across the studies, with few providing reproducible definitions or evidence of validation by medical records and/or rheumatologist's evaluation

Prognosis

The prognosis influences the clinical importance of symptoms and signs in patients not fulfilling criteria for a Classic/Accepted Disease. For this review the author's categorization was accepted. It is known that in most cases single symptoms or signs are not predictive of accepted connective diseases - for example polyarthralgias have numerous causes and rarely and in the majority no diagnosis is ever made (Williams, 1998; Mukerji, 1993). In patients presenting with monoarthritis of three months duration that do not have the associated features to meet the criteria for an accepted connective tissue diseases, the majority fail to attain a definitive diagnosis in the ensuing two years (Blocka, 1987). In patients with Raynaud's Phenomenon two studies have reported that only 3-19 % go on to attain diagnoses of defined connective tissue diseases (Harper, 1982; Fitzgerald, 1988; Williams, 1998).

The same is true of individuals with positive anti-nuclear antibodies. As described in the chapter on immunology, Aho et al showed that in healthy women less than one in 100 with a positive Anti-nuclear Antibodies will develop systemic lupus erythematosus. Schoenfield et al, found that over five years only 12% of women with a high level of Anti-nuclear Antibodies developed symptoms and none had developed an established connective tissue disease. Thus the evidence to date suggests that the majority of these symptoms and signs resolve spontaneously, and the abnormal laboratory tests do not lead to symptomatic disease in the majority of patients.

Strength of Association

Methodology

The same methods were applied as for the Classic/Accepted diseases and the results are listed below. The symptoms and signs in the eligible controlled studies were catagorized according to the Appendix

to Order 31E. Some categories included a number of different symptoms or signs. It should be appreciated that many studies do present the results as a frequency of symptoms rather than by individual women, so that women with multiple symptoms will be represented in several analyses

Study Results Reported for Symptoms

Nine cohort studies reporting endpoints, which could be classified according to the appendix of order 31 E were found. (Edworthy, 1998; Friis, 1887; Gabriel, 1994; Giltay, 1994; Kim, 1998; Nyren, 1998b; Park,1998; Wells,1994; Winther, 1998)

Symptoms are divided into the following categories:

1) Symptoms for which there are no data reported
2) Symptoms for which there is no study reporting an estimate with a lower confidence limit of greater than one (or the limit could not be calculated with information provided).
3) Symptoms for which there are discordant results (i.e. at least one but not all studies report an estimate with a lower confidence limit of greater than one).
4) Symptoms for which there are concordant results (i.e. all studies report an estimate with a lower confidence limit of greater than one).

1) Symptoms for which there are no data reported

Allergies
Bruising Easily
Burning In Chest/Heartburn/Esophageal Symptoms
Chronic Inflammation
Cognitive Dysfunction/Memory Problems
Coughing
Decrease in Sex Drive
Diarrhea
"Flu-Like" Feelings
Heart Palpitations
Hot Flashes
Incontinence
Infections
Malaise (General)
Muscle Cramps
Nausea/Vomiting
Night Sweats

Pain (Abdominal, Back, Chest, Intestinal, Joint, Muscle)-see arthralgias, myalgias
Sensitivity To Heat/Cold
Sleep Disorders
Sore Throat
Tenderness/Tender Points-see myalgias
TMJ problems
Urination - Frequency/Burning/Incontinence
Vision Problems - Blurred Vision/Light Sensitivity

2) Symptoms for which there is no study reporting a point estimate with a lower confidence limit of greater than one.

Alopecia

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: hair loss arms and legs
Frequencies: 0% cases in exposed group; 1% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 0.32 (0.01,8.30)

Breathing Difficulties/Shortness of Breath/Pulmonary Symptoms

Giltay 1994 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - age, year of operation

Endpoint: pleuritis
Frequencies: 4 cases in 235 exposed (1.7%); 5 cases in 210 unexposed (2.38%)
Relative Risk (adjusted/calculated): 0.71 (0.19, 2.63)

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: breathing difficulty
Frequencies: 2% cases in exposed group; 7% cases in unexposed group
Odds Ratio(adjusted/article): (Relative Risk not reported) 0.22 (0.067, 0.731)

Chronic Fatigue/Low Energy

Park 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Endpoint: fatigue

Factors Controlled: Design - Augmentation - "similar aged"; Reconstruction - partially matched on age, stage of disease and time of operation
Frequencies:
Augmentation -13 cases in 110 exposed (11.82%);
8 cases in 128 unexposed (6.25%)
Reconstruction -28 cases in 207 exposed (13.53%);
15 cases in 88 unexposed (17.05%)
Relative Risk (adjusted/calculated):
Augmentation - 1.89 (0.81, 4.39)
Reconstruction - 0.79 (0.45, 1.41)

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: <u>easily tired</u>
Frequencies: 15% cases in exposed group; 11% cases in unexposed group
Odds Ratio(adjusted/article): (Relative Risk not reported) 1.379 (0.547,3.310)

Concentration Difficulties

Edworthy 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Factors controlled: none

Endpoint: <u>thought problems</u>
Frequencies: 32% cases in exposed group; 17% cases in unexposed group
Relative Risk (adjusted/calculated): 1.88 (confidence interval not available)

Constipation

Park 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - Augmentation - "similar aged", Reconstruction - partially matched on age, stage of disease and time of operation

Endpoint: <u>constipation</u>
Frequencies:
Augmentation - 4 cases in 110 exposed (3.62%);
2 cases in 128 unexposed (1.56%)
Reconstruction - 8 cases in 207 exposed (3.82%);
4 cases in 88 unexposed (4.55%)
Relative Risk (adjusted/calculated):
Augmentation - 2.33 (0.43, 12.46)
Reconstruction - 0.85 (0.26, 2.75)

Fever (Low Grade)

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: persistent fever
Frequencies: 1% cases in exposed group; 0% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 1.099 (0.164, 7.381)

Headaches

Edworthy 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Endpoint: headache
Factors controlled: none
Frequencies: 18% cases in exposed group; 8% cases in unexposed group
Relative Risk (unadjusted/calculated): 2.25 (confidence interval not available)

Mood Swings/Irritability/Anxiety/Panic Attacks

Park 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - Augmentation - "similar aged"; Reconstruction - partially matched on age, stage of disease and time of operation

Endpoint: psychiatric
Frequencies:
Augmentation - 2 cases in 110 exposed (1.82%);
0 cases in 128 unexposed(0.0%)
Reconstruction - 3 cases in 207 exposed (1.45%);
1 cases in 88 unexposed (1.14%)
Relative Risk (adjusted/calculated):
Augmentation - 5.81 (0.28, 119.76)
Reconstruction - 1.28 (0.13, 12.09)

Mucosal Ulcers

Gabriel 1994 Study Type: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year; Analysis - age, index year

Endpoint: oral ulcers
Frequencies: 25 cases in 749 exposed (3.34%); 39 cases in 1498 (2.60%) unexposed
Relative Risk (adjusted/article): 0.69 (0.29, 1.63)

Giltay 1994 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - age, year of operation; Analysis - none

Endpoint: mouth ulcers for at least three weeks
Frequencies: 4 cases in 235 (1.70%) exposed; 2 cases in 210 (0.95%) unexposed
Relative risk (adjusted/calculated): 1.79 (0.33, 9.66)

Muscle Weakness

Gabriel 1994 Study Type: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year

Endpoint: symmetric muscle weakness
Frequencies: 1 case in 749 exposed (0.13%); 5 cases in 1498 unexposed (0.33%)
Relative Risk (adjusted/article): 0.43 (0.04, 2.67)

Neurologic Deficits

Nyren 1998b Study Type: Cohort
Implant Type: any
Factors Controlled: Design - none; Analysis - age, follow-up time for all endpoints except neuritis of the optic nerve, Guillian-Barre syndrome for which no factors were adjusted and amyotropic lateral sclerosis

Endpoint: diseases on nerve roots and plexuses
Frequencies: 3 cases in 7425 exposed (0.04%); 1 case in 3351 unexposed (0.03%)
Relative Risk (adjusted/article): 1.5 (0.6,3.9)

Endpoint: mononeuritis of the upper limb
Frequencies: 8 cases in 7425 (0.11%) exposed; 8 cases in 3351 unexposed (0.24%)
Relative Risk (adjusted/article): 0.5 (0.2,1.03)

Endpoint: mononeuritis of the lower limb
Frequencies: 7 cases in 7425 exposed (0.09%); 3 cases in 3351 unexposed (0.09%)
Relative Risk (adjusted/article): 1.3 (0.6,2.5)

Endpoint: Guillian-Barre syndrome
Frequencies: 1 case in 7425 exposed (0.01%); 0 cases in 3351 unexposed (0.0%)
Relative Risk (unadjusted/calculated): 1.35 (0.06, 33.23)

Endpoint: neuritis of the optic nerve
Frequencies: 0 cases in 7425 exposed (0.0%); 0 cases in 3351 unexposed (0.0%)
Relative Risk (unadjusted/calculated): 0.45 (0.01, 22.74)

Endpoint: amyotropic lateral sclerosis
Frequencies: 0 cases in 7425 exposed (0.0%); 0 cases in 3351 unexposed (0.0%)
Relative Risk (unadjusted/calculated): 0.45 (0.01, 22.74)

Winther 1998 Study Type: Cohort
Implant Type: unspecified
Factors Controlled: none

Endpoint: motor neuropathy
Frequencies: 0 cases in 1135 exposed (0.0%); 1 case in 7071 unexposed (0.01%)
Relative Risk (unadjusted/calculated): 2.08 (0.08, 50.91)

Endpoint: peripheral neuropathies
Frequencies: 9 cases in 1135 exposed (0.79%); 53 cases in 7071 unexposed (0.75%)
Relative Risk (unadjusted/calculated): 1.06 (0.52, 2.14)

Endpoint: optical retino- and neuropathy
Frequencies: 0 cases in 1135 exposed (0.0%); 1 case in 7071 unexposed (0.01%)
Relative Risk (unadjusted/calculated): 2.08 (0.08, 50.91)

Paraesthesia/Numbness and Tingling

Edworthy 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Factors controlled: none

Endpoint: numbness in extremities
Frequencies: 26% cases in exposed group; 15% cases in unexposed group
Relative Risk (unadjusted/calculated): 1.73 (confidence interval not available)

Swallowing Difficulties/Dysphagia

Park 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - Augmentation - "similar aged"; Reconstruction-partially matched on age, stage of disease and time of operation

Endpoint: dysphagia
Frequencies:
Augmentation - 2 cases in 110 exposed (1.82%);
0 cases in 128 unexposed (0.0%)
Reconstruction - 1 case in 207 exposed (0.48%);
0 cases in 88 unexposed (0.0%)
Relative Risk (adjusted/calculated):
Augmentation - 5.81 (0.28, 119.76)
Reconstruction - 1.28 (0.05, 31.21)

Swelling/Fluid Retention/Bloating

Park 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - Augmentation - "similar aged"; Reconstruction-partially matched on age, stage of disease and time of operation

Endpoint: edema
Frequencies:
Augmentation - 6 cases in 110 exposed (5.54%);
2 cases in 128 unexposed (1.56%)
Reconstruction - 32 cases in 207 exposed (15.46%);
20 cases in 88 unexposed (22.73%)
Relative Risk (adjusted/calculated):
Augmentation - 3.49 (0.72, 16.95)
Reconstruction - 0.68 (0.41, 1.12)

Vertigo/Dizziness/Ringing in Ears/Vestibular Dysfunction

Kim 1998 Study Type: Case-Control
Implant Type: silicone breast implants
Factors Controlled: Design-age

Endpoint: progressive sensorineural hearing loss or Meniere's disease
Frequencies: 5 exposures in 119 cases (4.20%); 3 exposures in 100 controls (3.0%)
Odds Ratio (adjusted/calculated): 1.45 (0.27, 9.54)

Nyren 1998b Study Type: Cohort
Implant Type: any
Factors Controlled: Analysis-age, follow-up time

Endpoint: Meniere's disease
Frequencies: 3 cases in 7425 exposed (0.04%); 1 case in 3351 unexposed (0.03%)
Relative Risk (adjusted/article): 0.8 (0.4, 1.4)

Winther 1998 Study Type: Cohort
Implant Type: unspecified
Factors Controlled: none

Endpoint: Meniere's disease
Frequencies: 1 case in 1135 exposed (0.09%); 3 cases in 7071 unexposed (0.04%)
Relative Risk (unadjusted/calculated): 2.08 (0.22, 19.95)

Weight gain

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: weight gain > 10 lbs
Frequencies:10% cases in exposed group; 3% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 1.307 (0.370, 4.619)

Weight loss

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: weight loss > 10 lbs
Frequencies:2% cases in exposed group; 4% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 0.419 (0.105, 1.676)

Park 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - Augmentation - "similar aged"; Reconstruction - partially matched on age, stage of disease and time of operation

Endpoint: weight loss
Frequencies:
Augmentation - 0 cases in 110 exposed (0.0%);
0 cases in 128 unexposed (0.0%)
Reconstruction - 4 cases in 207 exposed (1.93%);
2 cases in 88 unexposed (2.27%)
Relative Risk (adjusted/calculated):
Augmentation - 1.16 90.02, 58.09)
Reconstruction - 0.85 (0.16, 4.56)

3) Symptoms for which there are discordant results (i.e. at least one but not all studies report an estimate with a lower confidence limit of greater than one).

Arthralgias

Six studies reported arthralgias; some with increases in odds ratios, but only in Giltay 1994 did one of the analyses (of painful joints for at least three months) have a lower confidence limit exceeding 1 (1.37). The frequency of 8.5% in the unexposed group and of 19.57% in the exposed group are much higher than in other studies suggesting a different population.

Edworthy 1998	Study Type: Cohort Implant Type: silicone gel-filled Factors controlled: none Endpoint: hand pain Frequencies: 26% cases in exposed group; 18% cases in unexposed group Relative Risk (unadjusted/calculated): 1.44 (confidence interval not available)
Friis 1997	Study Type: Cohort Implant Type: any Factors Controlled: none Endpoint: arthritis not further specified Frequencies:2 cases in 2570 (0.08%) exposed; 8 cases in 11023 unexposed (0.07%) Relative risk (unadjusted/calculated): 1.07 (0.23, 5.05) Endpoint: rheumatism not further specified Frequencies: 1 case in 2570 exposed (0.04%); 1 case in 11023 unexposed (0.01%) Relative Risk (unadjusted/calculated): 4.29 (0.27,68.55)
Gabriel 1994	Study Type: Cohort Implant Type: any Factors Controlled: Design - age, duration of medical care, index year; Analysis - age, index year Endpoint: any arthritis (includes swelling of wrist, swelling of three or more joints, symmetric joint swelling or any other documented arthritis or synovitis) Frequencies:25 cases in 749 exposed (3.34%); 39 cases in 1498 unexposed (2.60%) Relative Risk (adjusted/article): 1.38 (0.84, 2.28)
Giltay 1994	Study Type: Cohort Implant Type: silicone gel-filled Factors Controlled: Design - age, year of operation; Analysis - none Endpoint: painful joints for at least three months Frequencies: 46 cases in 235 exposed (19.57%); 18 cases in 210 unexposed (8.57%) Relative risk (adjusted/calculated): 2.28 (1.37, 3.81) Endpoint: Swelling of joints for at least one week Frequencies: 14 in 235 (5.96%) exposed; 10 in 210 unexposed (4.76%) Relative Risk (adjusted/calculated): 1.25 (0.57,2.76)
Park 1998	Study Type: Cohort Implant Type: silicone gel-filled Factors Controlled: Design-Augmentation - "similar aged"; Reconstruction - partially matched on age, stage of disease and time of operation

Endpoint: joint pain
Frequencies:
Augmentation - 11 cases in 110 exposed (10.00%);
12 cases in 128 unexposed (9.38%)
Reconstruction - 31 cases in 207 exposed (14.98%);
13 cases in 88 unexposed (14.77%)
Relative Risk (adjusted/calculated):
Augmentation - 1.07 (0.49, 2.32)
Reconstruction - 1.01 (0.56, 1.84)

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: arthritis
Frequencies: 0% cases in exposed group; 1% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 1.159 (0.149, 9.040)

Endpoint: painful joints
Frequencies: 11% cases in exposed group; 5% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 1.929 (0.521, 7.142)

Endpoint: swollen joints
Frequencies: 5% cases in exposed group; 3% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 1.477 (0.263, 8.291)

Lymphadenopathy/Swollen and Tender Glands

Park did not find an association; Wells found a small increase in the frequency of swollen or tender glands under the arms with a lower confidence limit of 1.129 and 1.752 respectively. If this is a true increase, it is still not possible to know if these signs and symptoms occurred shortly after surgery or whether they were related to the primary indication for the implant.

Park 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - Augmentation - "similar aged"; Reconstruction - partially matched on age, stage of disease and time of operation

Endpoint: lymphadenopathy
Frequencies:
Augmentation - 1 case in 110 exposed (0.91%); 0 cases in 128 unexposed (0.0%)
Reconstruction - 0 cases in 207 exposed (0.0%); 1 case in 88 unexposed (1.14%)

Relative Risk (adjusted/calculated):
Augmentation - 3.49 (0.14, 84.73)
Reconstruction - 0.14 (0.01, 3.47)

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: swollen glands neck
Frequencies: 10% cases in exposed group; 5% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 1.982 (0.570, 6.894)

Endpoint: tender glands neck
Frequencies: 10% cases in exposed group; 7% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 1.433 (0.472, 4.354)

Endpoint: swollen glands under arm
Frequencies: 8% cases in exposed group; 1% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 7.082 (1.129,44.439)

Endpoint: tender glands under arm
Frequencies: 14% cases in exposed group; 3% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 6.898 (1.752, 27.154)

Myalgias

Friis 1997 is the only one of the three studies that has a raised odds ratios with a lower confidence limit that exceeds 1. Edworthy has a raised summary relative risk but the information was not available to allow a calculation of the confidence limits. This sample includes a variety of conditions including "muscular rheumatism, fibrositis and myalgia" so that these patients appear heterogeneous.

Edworthy 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Factors controlled: none

Endpoint: muscle pain
Frequencies: 25% cases in exposed group; 16% cases in unexposed group
Relative Risk (adjusted/calculated): 1.56 (confidence interval not available)

Friis 1997 Design: Cohort
Implant Type: any
Factors Controlled: none
Endpoint: muscular rheumatism, fibrositis, myalgia

Frequencies: 63 cases in 2570 exposed (2.45%); 169 cases in 11023 unexposed (1.53%)
Relative Risk (adjusted/calculated): 1.60 (1.20, 2.13)

Park 1998 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - Augmentation - "similar aged"; Reconstruction-partially matched on age, stage of disease and time of operation

Endpoint: muscle pain
Frequencies:
Augmentation - 7 cases in 110 exposed (6.36%);
7 cases in 128 unexposed (5.47%)
Reconstruction - 17 cases in 207 exposed (8.21%);
3 cases in 88 unexposed (3.41%)
Relative Risk (unadjusted/calculated):
Augmentation - 1.16 (0.42, 3.21)
Reconstruction - 2.41 (0.72, 8.01)

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: muscle pain
Frequencies:15% cases in exposed group; 9% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 1.396 (0.541, 3.600)

SICCA Symptoms (Dry Eyes/Mouth/Skin/Vagina)

Giltay 1994 found an increase frequency of 8.5% versus 1.9% in 52 cases with a relative risk of 2.20 and a lower confidence limit of 1.25 in the symptom of "regularly burning eyes"; Gabriel also found a slightly increased frequency of 3.3% versus 2.6% in five cases giving a relative risk of 1.42, but the confidence limits straddle 1(0.92, 2.21); however, these were for the symptoms of dryness of the eyes and mouth with no mention of the symptom of burning.

Gabriel 1994 Study Type: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year;
Analysis -(SICCA only) age, index year

Endpoint: salivary gland enlargement
Frequencies: 2 cases in 749 exposed (0.27%); 3 cases in 1498 unexposed (0.20%)
Relative Risk (adjusted/article): 1.42 (0.22, 7.98)

Endpoint: SICCA
Frequencies: 25 cases in 749 exposed (3.34%); 39 cases in 1498 unexposed (2.60%)
Relative Risk (adjusted/article): 1.42 (0.92, 2.21)

Giltay 1994 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - age, year of operation

Endpoint: regularly burning eyes
Frequencies: 37 cases in 235 exposed (8.51); 15 cases in 210 unexposed (1.90)
Relative risk (adjusted/article): 2.20 (1.25, 3.90)

Skin Changes/Rashes/Hives

Photosensitivity: Giltay 1994 reported an increased frequency of 'skin abnormalities worsened by sun exposure of 8.5% versus 1.9% relative risk of 4.47 (1.55, 12.86). Gabriel, found a frequency of 0.4% in exposed and unexposed. Park found a raised frequency in augmentation cases but a lower frequency in the reconstruction patients; this lack of consistency may be due to the small numbers of implants in this study leading to imprecise estimates.

Gabriel 1994 Study Type: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year;
Analysis - age, index year only for endpoint photosensitivity

Endpoint: malar or discoid rash
Frequencies: 1 case in 749 exposed (4.41%); 5 cases in 1498 unexposed (3.34%)
Relative Risk (adjusted/article): 0.43 (0.04, 2.67)

Endpoint: photosensitivity
Frequencies: 3 cases in 749 exposed (0.40 %); 6 cases in 1498 unexposed (0.40%)
Relative Risk (adjusted/article): 1.12 (0.28, 4.50)

Giltay 1994 Study Type: Cohort
Implant Type: silicone gel-filled
Factors Controlled: Design - age, year of operation

Endpoint: skin abnormalities worsened by sun exposure
Frequencies: 20 cases in 235 exposed (8.51%): 4 cases in 210 unexposed (1.90%)
Relative risk (adjusted/calculated): 4.47 (1.55, 12.86)

Park 1998 Study Type: Cohort
Implant Type: silicone gel-filled

Factors Controlled: Design - Augmentation - "similar aged"; Reconstruction - partially matched on age, stage of disease and time of operation

Endpoint: photosensitivity
Frequencies:
Augmentation - 5 cases in 110 exposed (4.55%);
3 cases in 128 unexposed (2.34%)
Reconstruction - 7 cases in 207 exposed (3.38%);
5 cases in 88 unexposed (5.68%)
Relative Risk (adjusted/calculated):
Augmentation - 1.94 (0.47, 7.93)
Reconstruction - 0.60 (0.19, 1.82)

Endpoint: telangiectasia
Frequencies:
Augmentation - 3 cases in 110 exposed (2.72%);
2 cases in 128 unexposed (1.56%)
Reconstruction - 2 cases in 207 exposed (0.97%);
1 case in 88 unexposed (1.14%)
Relative Risk (adjusted/calculated):
Augmentation - 1.77 (0.24, 15.41)
Reconstruction - 0.85 (0.06, 23.96)

Endpoint: rash
Frequencies:
Augmentation - 3 cases in 110 exposed (2.73%);
3 cases in 128 unexposed (2.34%)
Reconstruction - 8 cases in 207 exposed (3.68%);
8 cases in 88 unexposed (9.09%)
Relative Risk (adjusted/calculated):
Augmentation - 1.16 (0.24, 5.65)
Reconstruction - 0.43 (0.16, 1.10)

Endpoint: sclerodactyly
Frequencies:
Augmentation - 0 cases in 110 exposed;
12 cases in 128 unexposed
Reconstruction - 1 case in 207 exposed;
0 cases in 88 unexposed
Relative Risk (adjusted/calculated):
Augmentation - 0.05 (0.00, 0.78)
Reconstruction - 1.28 (0.05, 31.21)

Endpoint: abnormal pigment
Frequencies:
Augmentation - 2 cases in 110 exposed (1.82%);
2 cases in 128 unexposed (1.56%)

Reconstruction - 3 cases in 207 exposed (1.45%);
1 case in 88 unexposed (1.14%)
Relative Risk (adjusted/calculated):
Augmentation - 1.16 (0.17, 8.12)
Reconstruction - 1.28 (0.13, 12.09)

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: rashes
Frequencies:4% cases in exposed group; 4% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 1.067 (0.273, 4.168)

Endpoint: skin thickening
Frequencies: 2% cases in exposed group; 7% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 0.206 (0.043, 0.992)

Endpoint: skin tightness
Frequencies: 12% cases in exposed group; 19% cases in unexposed group
Odds Ratio (adjusted/article): (Relative Risk not reported) 0.582 (0.264, 1.284)

Stiffness

Gabriel 1994 found an increased frequency of 4% versus 2.3% with a relative risk of 1.80 and a lower confidence limit of 1.0. The significance and importance of this is unclear. Wells 1994 did not find an association.

Gabriel 1994 Study Type: Cohort
Implant Type: any
Factors Controlled: Design - age, duration of medical care, index year; Analysis - age, index year

Endpoint: morning stiffness
Frequencies: 30 cases in 749 exposed (4.01%); 35 cases in 1498 unexposed (2.34%)
Relative Risk (adjusted/article): 1.80 (1.10, 2.93)

Wells 1994 Study Type: Cohort
Implant Type: silicone breast implants
Factors Controlled: Analysis - age, year of operation

Endpoint: general stiffness
Frequencies:10% cases in exposed group; 10% cases in unexposed group

Odds Ratio (adjusted/article): (Relative Risk not reported) 0.930 (0.382, 2.265)

Symptoms for which there are consistent results

None

Few studies have adequate numbers of patients, and although some individual studies show some degree of elevation of relative odds or relative risks, these are not substantial in a consistent fashion in any of these conditions.

VI. Concluding Comments

In this chapter the clinical case definitions have been reviewed for the three clinical categories of Classic/Accepted Diagnosis., Atypical Presentations of Connective Tissue Diseases, and Symptoms and Signs listed in the Appendix to the Court Order 31E. The prognosis of many of the Classic/Accepted diseases is poor with most patients being subjected to sustained morbidity with symptoms, reduction in ability to carry out their activities of daily living and reduced psychosocial well-being.

In none of the Classic/Accepted diagnosis was there any 'appreciable' association (as defined in the Epidemiology Chapter) with silicone breast implants demonstrated.

The atypical syndrome of Undifferentiated Connective Tissue Disease (UCTD) as defined by the criteria of Williams, also has sustained morbidity in a proportion of patients. In the one study of this, there were few implants and no appreciable association was found.

Patients with one or more symptoms and signs but who do not meet the criteria for a specified Classic/Accepted connective tissue disease or the criteria for UCTD as defined by Williams, have a better prognosis and do not usually progress to a defined disease. There are few symptoms and signs for which a single study found an appreciable association, but in all cases there were other studies of the same symptom or sign that did not confirm this association. Additional caution in accepting any association in these studies is needed compared to the studies of the Classic/Accepted diagnosis and UCTD, since different symptoms are included in some of the categories, the numbers of cases are small, a single woman with more than one symptom will be represented in the analysis of each symptom that the woman has experienced.

Other atypical syndromes have been suggested, some of which include the presence of a silicone breast implant and none of which (with the exception of UCTD as stated above) have stringent, objective diagnostic criteria. Including the exposure (i.e. breast implants), in the disease definition precluded the rigorous scientific evaluation of this proposed entity, since there is no possibility of comparing women with and without the syndrome to estimate each group's frequency of implants. Furthermore, many of the signs and symptoms including the rheumatologic and psychological complaints are so common in the general population and as presenting complaints in physician's offices, that a possible increased frequency of these complaints among those with implants would be difficult to discern.

The literature submitted by the court was reviewed for information on the effect of silicone breast implants on the clinical course and immunologic parameters in women with diagnosed connective tissue disease. No substantive data was found that allowed a rigorous assessment of any differences in the clinical course from those with the conditions but without implants; thus no conclusion can be reached due to the uncertainty arising from a lack of research addressing this question.

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Table 1: Description of Included Studies

Study	Methods	Participants	Interventions	Outcomes
Burns (1996)	**Case Control Study** **Study Dates** Cases of scleroderma diagnosed between 1985-1991. Data collection August 1992 – May 1993. **Group Selection** Case Definition: Women diagnosed with systemic sclerosis in Michigan between 1985-1991 were recruited from hospitals, rheumatologists and United Scleroderma Foundation. Control Definition: Females, identified through random digit dialing, were frequency matched to cases on age (5 yr. Intervals), race and geographic region. **Group Determination** Cases: medical records were reviewed by a rheumatologist to determine eligibility Controls: self report (telephone interview) **Ascertainment of Exposure** Cases: self report (telephone interview) Controls: same To determine the accuracy of self reporting of breast implants a validation study was carried out on a separate population. (94% accurate with respect to presence or absence of implant) **Blinding** Subjects were unaware of the research hypothesis and in the case of the validation study, investigators were blind to implant status.	**Country**: Michigan USA **Cases**: N = 274 **Controls**: N = 1184 Mean age at interview: cases 54.3 years, controls 52.6 years. Income >$ 15,000: cases 74.8 %, controls 81.5% (p<.05) High school education: cases 85% , controls 84.3% Race - non black: cases 83.9%, controls 88.1% Reconstruction due to breast cancer: cases 50%, controls 50% Separate analysis for breast cancer subjects: no Years since implantation: cases (n=2) 1 and 12 years., controls (n=14) median 8.8 years Cases with breast implants: 0.7% Controls with breast implants: 1.2% **Response Rate** Cases: Investigators estimate that 80 - 87% of incident cases in Michigan from 1985-91 were identified. 75-80% of these responded to mailing, 93% of whom agreed to participate. Controls: 80%	**Implant Type** Unspecified: N = 1(control) Silicone gel filled: N = 14 (2 cases, 12 controls) Saline: N = 1 (control) Polyurethane coated: N = 2 (controls) Separate analysis for Silicone gel filled implants: yes **Exposure** Rupture described: yes (1 case had ruptured;no ruptures reported among controls although 6 experienced encapsulation, hardness, scar tissue or unspecified problems) Explantation described:no Duration described:yes Excluded injections: no (they were enumerated as "injections to a body part" and reported separately)	**Diagnosis** Systemic sclerosis (1980 ACR criteria or subject exhibited signs and symptoms characteristic of SSc: sclerodactyly or thick tight skin, and at least one other manifestation of CREST. Excluded linear or localized SSc – morphea)

Study	Methods	Participants	Interventions	Outcomes
Dugowson (1992)	**Case Control Study** **Study Dates** Not reported **Group Selection** Case Definition: Women with new onset of rheumatoid arthritis Control Definition: Similarly aged women were recruited co-operatively with a breast cancer study **Group Determination** not reported **Ascertainment of exposure** Cases: self report (questionnaire) - history of implants prior to reference date (first physician visit for rheumaroid arthritis) Controls: self report (questionnaire) - history of implants prior to a reference date chosen randomly from cases **Blinding** not reported	**Country**: Seattle, Washington USA **Cases**: N = 300 **Controls**: N = 1456 Cases with breast implants: 0.3% Controls with breast implants 0.8% **Response Rate** Cases: 86%, Controls: Number of subjects in original pool from which controls were drawn is not reported	**Implant Type** Unspecified **Exposure** Rupture described: no Explantation described: no Duration described: no Excluded injections: not reported	**Diagnosis** Rheumatoid Arthritis (criteria not reported)

Study	Methods	Participants	Interventions	Outcomes
Edworthy (1998)	**Retrospective Cohort Study** **Study Dates** 1978-1986 – Subjects were identified who underwent cosmetic surgery during this period. No dates reported for recruitment and examination of these women. 1982-1993 - data base searched for hospitalization rates and service use during this time period. **Group Selection** Exposed: Women, identified through the Alberta Health Registry, who had obtained breast implants, other than for reconstructive purposes, between 1978 and 1986. Unexposed: Women, from the same source, who had undergone non silicone related cosmetic surgery. **Group Determination** Exposed: Alberta Health Registry procedural codes, medical records (for verification of implant type), self report (questionnaire) Unexposed: Alberta Health Registry procedural codes, self report **Ascertainment of Outcome** Exposed: Direct measurement (physical exam for those with a history or symptoms of disease), lab values, self report (questionnaire and for those attending physical exam, a detailed history) Unexposed: same **Blinding** Rheumatologist's Physical assessment	**Country**: Alberta, Canada **Exposed**: N = 1,576 **Unexposed**: N = 727 Median Age at Assessment: Exposed (Silicone gel filled) 42 years, Unexposed 46 years Median Years of Education: Exposed 12, Unexposed 13 Married: Exposed 80.1, % Unexposed 73.7% Mean Duration of Exposure: 13.5 years Reconstruction Due to Breast Cancer: 0% **Response Rate** Of the 9200 implantations and 7400 other cosmetic surgeries identified, 60% had a current address. Of those contacted 3152 implanted women 34% of those identified) and 2670 controls (36% of those identified) responded. Of those who responded, 41% of implanted subjects and and 69% of controls declined. An additional 9% of implanted subjects and 4% of controls were ineligible.	**Implant Type** Unspecified (N=86) Silicone gel filled (N=1,112) Saline (N=352) Meme (N=26) Only Silicone gel filled implants appear to have been included in the analyses. **Exposure** Rupture Described: no Explantation Described: no Duration Described: yes Excluded Injections yes	**Diagnosis** Rheumatoid Arthritis (ACR tree criteria) Systemic Lupus Erythmatosis (ARA 4 of 11 criteria) Scleroderma (ACR criteria, CREST or variants of) Sjogrens Syndrome (clinical signs of dry eyes, dry mouth, history of parotitis), Atypical Connective Tissue Disease (cases which did not conform to expected patterns of presentation and had a greater than 50% certainty of having any CTD) **Lab Values** ANAs (indirect immunofluorescence using HEp-2 cells, considered positive if > 1:40 dilution) **Symptoms** Thought problems Numbness in extremities Muscle pain Headache Hand pain

Study	Methods	Participants	Interventions	Outcomes
Englert (1996)	**Case Control Study** (Update of Englert 1994) **Study Dates** Study initiated 1989. Scleroderma diagnosis must have been made prior to Dec 31,1988 (study time frame 1974-1988) Controls must have attended General practitioner since Jan 1990. **Group Selection** Case Definition: Patients with SSc who resided in Sydney for at least 6 consecutive months within study time frame. Excluded were patients with mixed CTD morphea or other localized forms of SSc. Cases were recruited from hospitals, death certificates, physicians, Scleroderma Association of NSW and medical laboratories performing ANA tests. If patient migrated to Sydney, the major reason must not have been for scleroderma management, and the diagnoses must have been made prior to emigration Control Definition: Sydney residents (for at least 6 consecutive months) were recruited from 28 randomly selected general practices and were age and sex stratified (5 years) with a living case. Those with scleroderma CREST or a psychiatric history were excluded. **Group Determination** Cases: medical records Controls: medical records **Ascertainment of Exposure** Cases: medical records (GP and for those with implants surgeon's records) for deceased and medical records plus self report (interview) for living subjects Controls: medical records plus self report (interview)	**Country**: Sydney, Australia **Cases**: N = 532 **Controls**: N = 253 Explantation: cases 50%, controls 20% Dates of implantation: cases 1978-1983, controls 1973-1990 Cases with breast implants: 0.9% Controls with breast implants: 1.2 -1.6% **Response Rate** not reported	**Implant Type** Unspecified 10% Silicone gel filled 80% (analysed separately) Saline:10% **Exposure** Rupture described: no Explantation decribed: yes Duration described: yes Excluded injections: not reported	**Diagnosis** Systemic Sclerosis (ACR criteria or patient had sclerodyctaly plus 2 of the following: Raynaud's phenomenon, oesophageal dysmotolity, calcinosis, telangiectasia(e), bilateral basal pulmonary fibrosis or elevated ANA)

Blinding
Both physicians and patients were blind to each others responses regarding mammoplasty status.

Study	Methods	Participants	Interventions	Outcomes
Friis (1997)	**Retrospective Cohort Study** **Study Dates** Identification of subjects 1977-1992 Follow up to Dec31/93 **Group Selection** Exposed: Women from Danish Central Hospital Register who had received implants between 1977 and 1992 for cosmetic or reconstructive purposes. Unexposed: Women from the same source who had undergone breast reduction surgery or correction for mammoptosis or women who had been diagnosed with breast cancer but had not received an implant. Breast cancer controls were matched to the reconstruction patients in: age, disease (localized, regional, metastatic), and calendar time (5 years) **Group Determination** Exposed: medical records (information on breast surgery confirmed by authors) Unexposed: same as exposed **Ascertainment of Outcome** Exposed: medical records (diagnosis of definite CTD validated by rheumatologists) Unexposed: same as exposed **Blinding** Not reported	**Country**: Denmark **Exposed**: cosmetic N = 1,335, reconstruction N = 1,435 **Unexposed**: breast reduction N = 7,071, mamoptosis N = 472 (not analysed), breast cancer N= 3,952 Median Age at Entry: Exposed: cosmetic 31years, reconstruction 45 years; Unexposed: reduction 31 years, mamoptosis 28 years, breast cancer 47years Median Length of Follow up: Exposed: cosmetic 8.4 years; reconstruction 7.2 years Unexposed: reduction 7.6 years, mamoptosis 6.2 years, breast cancer 5.3 years Reconstruction due to breast cancer: 52% (analysed separately) **Response Rate** All eligible women from the register were entered into the study. They were followed until the time of death, emigration or Dec 31 1993, whichever came first.	**Implant** Unspecified:16% Silicone gel filled: 84% (no separate analysis) Note: Percentages are based on an earlier sampling study **Exposure** Rupture described: no Explantation described: no Duration described: no Excluded Injections: not reported	**Diagnosis** (All cases represented rheumatic disease requiring hospitalization and were classified according to ICD 8) Rheumatoid Arthritis (ICD 712.09 -39, 712.59) Dermatomyositis / Polymyositis (ICD 716.09, 716.19) Systemic Sclerosis (ICD 734.0-.09) Systemic Lupus Erythematosis (ICD 734.19) Sjogrens Syndrome (ICD 734.90) Polymyalgia Rheumatica and Temperal Arteritis (446.30-39) Muscular Rheumatism Including Fibrositis and Myalgia (717.90 717.99) Arthritis Not Further Specified (715.99) Rheumatism Not Further Specified (718.99) CTD Not Further Specified (734.91, 734.99)

Study	Methods	Participants	Interventions	Outcomes
Gabriel (1994)	**Retrospective Cohort Study** **Study Dates** Exposed: implantation occurred between January 1964 to December 1991 Follow up: to December 31 1991 **Group Selection** Exposed: All women in Olmstead county whose medical records indicated that they had received a breast implant. Unexposed: Age matched (3 years) Olmstead women who had undergone a medical evaluation within 2 years of date of matched case implantation. For each woman who had undergone reconstruction following mastectomy for breast cancer an additional 2 controls were selected who had undergone mastectomy but had not received an implant (analysis of data using this control group was not reported). **Group Determination** Exposed:medical records Unexposed: same **Ascertainment of Outcome** Exposed: Medical records reviewed by trained nurses for evidence of clinical features, and laboratory and radiographic studies necessary to make diagnoses. Unexposed: same **Blinding** Not reported	**Country**: Olmsted county,Minnesota USA **Exposed**: N = 749 **Unexposed**: N = 1498 Mean age: exposed 34.4 +/- 10.5 years, unexposed 34.3 +/- 10.5 years Caucasian: exposed 96.8%, unexposed 92.8% ($p<.05$) Marital status - single: exposed 15.2%, unexposed 21.0% ($p<.05$) History of smoking: exposed 53.5%, unexposed 45.6% ($p<.05$) Mean years since implantation or index visit: exposed 7.8 +/- 5.5 years, unexposed: 8.3 +/- 5.8 years (36% of cohort followed for at least 10 years) Reconstruction Due to Breast Cancer: 17% (analysed both separately and combined) Bilateral implants: 83% **Response Rate** All eligible records included. Follow up continued to Dec 31 1991, death or date of last health care visit.	**Implant Type** Unspecified:N=2 Silicone gel filled: 78.3% Saline: 5.2% Double Lumen: 6.7% Polyurethane coated: 9.6% Combination of Silicone and Saline: 6.7% Perras Papillion:N=2 **Exposure** Rupture described: no Explantation described: no Duration described: yes. 23.6 % of exposed women had undergone >1 surgical breast implantation procedure Excluded Injections: yes	**Diagnosis** determined from clinical features, lab and radiographic studies Systemic sclerosis (ACR criteria) Rheumatoid arthritis (ACR criteria) Scleroderma (ACR criteria) Sjogrens SLE Dermatomyositis Polymyositis Vasculitis Ankylosing spondylitis Psoriatic arthritis Arthritis associated with inflammatory bowel disease Polychondritis Polymyalgia rheumatica Any CTD (combined endpoint including all of the above) Hashimoto's thyroiditis Primary bilary cirrhosis Sarcoidosis **Lab Values** Antinuclear Antibodies (values considered abnormal at the time the test was performed) **Symptoms** any arthritis (swelling of the wrist, swelling of 3 or more joints, symmetric joint swelling or any other documented arthritis or synovitis) SICCA (dry eyes, dry mouth, or keractoconjunctivitis) serositis (serosal inflammation such as pleuritis and pericarditis) malar or discoid rash oral ulcers photosensitivity salivary gland enlargement symmetric muscle weakness morning stiffness

Study	Methods	Participants	Interventions	Outcomes
Giltay (1994)	**Retrospective Cohort Study** **Study Dates** Surgery performed Jan 1978 – Dec 1990. Questionnaire regarding rheumatic symptoms June 1992 **Group Selection** Exposed: All patients who received silicone breast implants at Free University Hospital, Amsterdam. Unexposed: Age matched females who had an operation not involving silicone in the same year in the same department. **Group Determination** Exposed: medical records, Unexposed: same **Ascertainment of Outcome** Exposed: Self report – mailed questionnaire and for those suspected of rheumatic disease, medical records Unexposed: same **Blinding** Not reported	**Country**: The Netherlands **Exposed**: N = 235 **Unexposed**: N = 210 Mean age: exposed 43 years ; unexposed 43 years Mean years since implantation: 6.5 years (range 2-14 years) for all subjects Mean interval between surgery and symptom onset: exposed 5.1years unexposed 5.9 years Reconstruction due to breast cancer: 23.8% (not analysed separately) Bilateral: 68.5% **Response Rate** Exposed 82% Unexposed 73%	**Implant Type** Implant: Silicone gel filled excluded polyurethane coated **Exposure** Rupture described: no Explantation described: no Duration described: yes Excluded Injections: yes	**Diagnosis** Probable inflammatory disease with onset 1 or more years following surgery (subjects self reported symptoms on questionnaire were assessed by rheumatologist regarding likelihood to have disease; likely subjects were further assessed via phone, plus medical records; criteria not reported.) **Symptoms** Raynaud's phenomenon painful joints (> 3 months) swollen joints (1+ weeks) regularly burning eyes mouth ulcers (3+ weeks) pleuritis skin abnormalities worsened by sunlight combined endpoint - subjects with at least one symptom arising after surgery

Study	Methods	Participants	Interventions	Outcomes
Goldman (1995)	**Cross Sectional Study** **Study Dates** 1982 - May 1992 - Medical records of office visits between these dates provided data regarding both exposure and outcome. (1982-1986 prior to computerization - some incomplete data) **Group Selection** Both exposed and unexposed subjects were identified from all female patient records in one referral based rheumatology practice. **Group Determination**: Exposed: Medical records - historical, physical or radiologic evidence of a breast implant. Unexposed: Medical records - no evidence of breast implant **Ascertainment of outcome** Exposed: Medical records - independent chart review to confirm rheumatological diagnoses Unexposed: same **Blinding** Not reported	**Country**: Atlanta , Georgia USA **Exposed**: N = 150 **Unexposed**: N = 4079 Mean age (at 1st visit): exposed: 43.8, unexposed 47.2 ($p<.04$) SES (mean income based on ZIP code): exposed $43,744, unexposed $39,524 ($p<0.0001$) Race "primarily Caucasian" Mean years since implantation: exposed who did develop disease 8.3, exposed with no disease 9.9 % of cohort with breast implants: 3.5 **Response Rate** 100% of eligible records reviewed	**Implant Type** Unspecified (11%) Silicone gel filled (85%) (no separate analysis) Saline (4%) **Exposure** Ruptured described: no Explantation described: no Duration described: yes Injections excluded: yes	**Diagnosis** Patients were diagnosed according to ACR and Arthritis Foundation criteria. No year was reported for ICD codes. Rheumatoid Arthritis (ICD 714) Systemic Lupus Erythematosus (ICD 710.0) Systemic Sclerosis - including CREST (ICD 710.1) Sjogrens (ICD 710.2) Dermatomyositis / Polymyositis (ICD 710.3, 710.4) Mixed Connective Tissue Disease (ICD 710.9) Rheumatoid Arthritis and Connective Tissue Disease (combined endpoint comprised of all the above)

Study	Methods	Participants	Interventions	Outcomes
Hennekens (1996)	**Cross Sectional Study** **Study Dates** Sept 1992 - May 1995 - Questionnaire regarding both exposure and disease was mailed to prospective participants. Aug 1, 1995 - forms completed Dec 31 1991 - only CTDs diagnosed prior to this date were included in the analysis. **Group Selection** Female health professionals age 18 - 99 residing in the USA or Puerto Rico, who completed mailed questionnaires for participation in the Women's Health Study. Excluded were women who reported an implant or CTD prior to 1962 or who provided unclear or missing information regarding implant surgery, CTD and dates **Ascertainment of Exposure** Exposed: self report (questionnaire) - women who reported ever having had a breast implant along with the year of procedure Unexposed: self report (questionnaire) - those not reporting an implant **Ascertainment of Outcome** Exposed: self report (questionnaire) Unexposed: same **Blinding** Not reported	**Country**: USA and Puerto Rico **Exposed**: N = 10,830 **Unexposed**: N = 384,713 Mean age: 51.7 years. Caucasian: 90.7% Reconstruction due to breast cancer: 18% (estimated from report of implantation the same year as diagnosis of breast cancer. No separate analysis of these cases) Cohort with breast implants: 3.6% **Response Rate** 24% (whole cohort)	**Implant Type** Unspecified **Exposure** Rupture described: no Explantation described: no Duration described: yes Excluded Injection: no	**Diagnosis** All diseases were self reported. No diagnostic criteria were used Rheumatoid Arthritis Systemic Lupus Erythematosus Sjogrens Dermatomyositis / Polymyositis Other Connective Tissue Disease (including Mixed) Any Connective Tissue Disease (combined endpoint comprised of all the above)

Study	Methods	Participants	Interventions	Outcomes
Hochberg (1996)	**Case Control Study** **Study Dates** July 1990 – summer of 1991 - eligible cases mailed questionnaires.1993 - data collected from an additional 18 of the eligible cases Dec 1991 – cases diagnosed after this date were excluded July 1993 – Dec 1994 – controls interviewed **Group Selection** Case Definition: Women with a clinical diagnosis of SSc Identified at 3 university based scleroderma research centers: 1) Baltimore-Washington – seen at scleroderma center, referred by rheumatologists, or members of Scleroderma Foundation; 2) Pittsburgh – all patients seen by faculty members at U of Pittsburgh were consecutively enrolled; 3) San Diego/Orange County - patients followed by faculty members UCSD or community based rheumatologists. Patients < 18 years at diagnoses or Residing outside USA were excluded. Control Definition: Race and sex matched local controls were identified through random digit dialing and frequency matched to cases in 3 strata: age < 45, 45-64 and 65+. Women with a self reported diagnosis of CTD were excluded. **Group Determination** Cases: medical records Controls: self report (telephone interview **Ascertainment of exposure** Cases: self report (self administered questionnaire)	**Country**: USA (Multicentre) **Cases**: N = 837 **Controls**: N = 2507 Mean Age at Interview: cases: 55.3 +/- 12.9 years controls: 55.6 +/- 15. 5years SES - % High School Graduates: cases 86.6%, controls: 85.3% % Caucasian: cases 90.4%, controls 90.9% Mean Duration of SSc: cases 10.0 +/- 7.2 Median years since implantation: cases: 11 years (time to disease), controls: 10 years (time to interview) Complications related to implants: Cases 0%, Controls 16% (hardening N=2, shifting N=2, leakage N=1) Explantation: cases 36% (Diagnosis of scleroderma N=2, hardening N=1, leakage N=1) controls .032% (breast pain N=1) Breast surgery (related to benign breast masses, breast cancer, fibrocystic disease and mastitis): cases 17.9%, controls 18.5% Cases with implants: 1.3 % Controls with implants: 1.2% **Response Rate** Cases: Baltimore 61.9% Pittsburg 78.4% San Diego 100% Controls: 90% of those eligible	**Implant Type** Silicone gel-filled **Exposure** Rupture described: yes Explantation described: yes Duration described: yes Excluded Injections: yes	**Diagnosis** Systemic Sclerosis (no diagnostic criteria reported)

	Controls: self report (telephone interview) **Blinding** Not reported

Study	Methods	Participants	Interventions	Outcomes
Kim (1998)	Case Control Study **Study Dates** Questionnaires collected between July 1995 and Jan 1996 **Group Selection** Case Definition: Female patients with a diagnosis of either Meniere's disease or progressive sensorineural hearing loss who had undergone prior Western blot analysis for reactivity to 68 kD. Control Definition: Women waiting for outpatient lab results at an ambulatory care center matched to cases on age. **Group Determination** Cases: Identified from a single clinical practice. Controls: Mailed questionnaire. Those reporting a history of hearing loss were excluded. Ascertainment of Outcome Cases: Self report – mailed questionnaire. Controls: questionnaire **Blinding** not reported	**Country**: La Jolla California USA **Cases**: N=119 **Controls**: N=100 Mean Age: cases - Meniere's – 48.5 years, cases – PSNHL – 50.2 years controls 49.7 years Mean time from implantation to disease: 9.23 years (range 2 months to 24 years) Cases with breast implants: 4.2% Controls with breast implants: 3% **Response Rate** Cases: 64.7% Controls: not reported	**Implant Type** "Silicone breast implants" **Exposure** Rupture described: no Explantation described: no Duration described: no Injections excluded: yes	**Diagnoses** Meniere's Disease (no criteria reported) Progressive Sensorineural Hearing Loss (PSNHL, no criteria reported) **Lab Values** Anti-68kD antibodies (Western blot analysis) – This variable was analysed both on its own and in combination with Meniere's Disease or PSNHL

Study	Methods	Participants	Interventions	Outcomes
Lacey (1997)	**Case Control Study** **Study Dates** 1985 - 1992 diagnosis of SSc **Group Selection** Case Definition: Women diagnosed with SSc in Ohio Control Definition: Ohio women selected by random digit dialing matched to cases on age geographic location and race **Group Determination** Cases: medical records – reviewed by rheumatologist Controls: self report **Ascertainment of Exposure** Cases: self report - telephone questionnaire Controls: self report - telephone questionnaire **Blinding** Blind expert reviewed self reported exposure data	**Country**: Michigan USA **Cases**: N = 189 **Controls**: N = 1043 Cases with implants: 1.1% Controls with implants: 1.2% **Response Rate** Not reported	**Implant Type** Unspecified N=4 Silicone gel filled N=11 (separate analysis provided) **Exposure** Rupture described: no Explantation described : no Duration described : no Excluded injections: no (data re injections was recorded but does not appear to have been analysed)	**Diagnosis** Systemic Sclerosis (1980 ACR criteria or subject exhibited signs and symptoms characteristic of SSc: sclerodactyly or thick tight skin, and at least one other manifestation of CREST - Excluded linear or localized SSc – morphea)

Study	Methods	Participants	Interventions	Outcomes
Liang (1996)	**Case Control Study** **Study Dates** Diagnoses 1980-1992 **Group Selection** Case Definition: All women 18+ years in Michigan and Ohio Diagnosed with UCTD between 1980 and 1992 Control Definition: Identified through random digit dialing. Frequency matched to cases within each state on age race and geographic location. **Group Determination** Cases: medical records - National Hospital discharge database, university hospital databases, mailing list of rheumatologists, Scleroderma Foundation Controls: self report **Ascertainment of Exposure**: Cases: self report - telephone interview Controls: self report - telephone interview **Blinding** Yes - blind review of self reported occupational hobby exposure	**Country**: Michigan and Ohio, USA **Cases**: N = 205 **Controls**: N = 2220 Mean age at interview: Cases: 52.3 Controls: 51.4 Mean age at diagnoses: cases 41.6, Caucasian: cases 90.7%, controls 89.4% Cases with breast implants: 1.5% Controls with breast implants: 1.2% **Response Rate** Not reported	**Implant Type** Unspecified **Exposure** Rupture described: no Explantation described: no Duration described: no Excluded injections: not reported	**Diagnosis** Undifferentiated Connective Tissue Disease (Either the referring physician diagnosis or HCIA discharge code was UCTD (ICD 9 10.9) or the patient fulfilled all of the following: 1) was diagnosed as having Systemic Sclerosis but did not meet the ACR criteria, 2) did not meet the diagnostic criteria for another CTD and 3) had a minimum of 2 signs, symptoms or lab values suggestive of a CTD.)

Study	Methods	Participants	Interventions	Outcomes
MacDonald (1996)	**Case Control Study** **Study Dates** Diagnosis: Post Jan 1988 Interviews conducted Oct/93 – Jun/94 **Group Determination** Case Definition: patients from the Minnesota Regional CFS Research Program Registry whose disease onset occurred after Jan 1988 and were residents of Minneapolis St. Paul or St. Cloud. They were diagnosed after medical psychometric and psychiatric assessment could not establish another explanation for fatigue. Two investigators, a psychiatrist and an infectious disease specialist, had to agree on the diagnosis. Control Definition: matched to cases on neighborhood (calling households with same 3 digit prefix as cases) gender and age (5 years) **Group Determination** Cases: medical records Controls: self report – telephone interview **Ascertainment of Exposure** Cases: self report – telephone interview Controls: self report – telephone interview **Blinding** Not reported	**Country**: Minnesota USA **Cases**: N = 35 **Controls**: N = 35 Median Age at Disease Onset: cases 37 Median Duration of Illness: cases 54.3 months Mean Years Since Implantation: cases 11, controls not reported Subjects with any breast implant: cases 3%, controls 6% Reconstruction due to breast cancer: not reported **Response Rate** Cases: 83% Controls: 58%	**Implant Type** Silicone gel filled (1 case 1 control - numbers available to analyse separately) Saline (1 control) **Exposure** Rupture described: no Explantation described: no Duration described: yes Excluded injections: not reported	**Diagnosis** Chronic Fatigue Syndrome (8 of 10 symptoms identified in 1988 CDC criteria, more than once or persistently for at least 6 months)

Study	Methods	Participants	Interventions	Outcomes
Nyren (1998)	**Retrospective Cohort Study** **Study Dates** Breast surgery took place from 1965 – 1993 Follow up from Jan 1 1972 – Dec 31 1993 **Group Selection** Exposed: All records in the National Swedish Inpatient register that contained the surgical code for breast augmentation with foreign material. These were divided into 2 subcohorts - those with a diagnosis of breast cancer and those who had received implants for other reasons (mainly cosmetic) Unexposed: All records, of patients who had received breast reduction surgery, were selected from the same source. From these, 1 woman was selected as a control for each subject in the cosmetic implant group. They were matched on age (5 years), hospital and calendar year at operation (2 years). **Group Determination** Exposed: Medical records – National Swedish Inpatient Register Unexposed: same **Ascertainment of Outcome** Exposed: Medical Records – records were reviewed to confirm diagnoses Unexposed: same **Blinding** Not reported	**Country**: Sweden **Exposed**: N = 7442 **Unexposed**: N = 3353 Mean years since operation: exposed cosmetic 10.3 years, exposed reconstruction 6.0 years, unexposed: 9.9 years Reconstruction Due to Breast Cancer: 53 (separate analysis provided) **Response Rate** Medical records - 100% of those eligible. Censoring occurred at date of immigration, death or end of follow up.	**Implant Type** Unspecified 7% Silicone gel filled 56% (no separate analysis) Saline 24% Double Lumen 12% Polyurethane Coated <0.1% **Exposure** Rupture Described: no Explantation Described: no Duration Described: yes Excluded Injections: not reported	**Diagnosis** Determined via ICD 8 and ICD 9 codes in Swedish Inpatient Register Sjogrens Syndrome (ICD 8 734,90, ICD 9 710C) Systemic Lupus Erythematosis (ICD8 734,10 ICD9 710A) Systemic Sclerosis (ICD8 734,00,01,09 ICD 9 710B) Dermatomyositis (ICD8 716,00 ICD 9 710D) Rheumatoid Arthritis (ICD8 712,00,10,20,38,39 ICD9 714A,B,C,D 719D) All Definite CTD (combined outcome included the proceeding diagnoses) Fibromyalgia (ICD8 712,50 717,98 718,99 ICD 9 729A) Polymyositis (ICD 8 716.10, ICD 9 710E) Polymyalgia Rheumatica (ICD 8 446.38, ICD 9 725) Polyarteritis Nodosa (codes na) Temporal Arteritis (ICD 8 446.30, ICD 9 446F) Other Specified CTD (ICD 8734.98, ICD 9710W) CTD or Collagenosis without further specification (ICD 8 734.91,734.99, ICD 9710) Sarcoidosis (ICD 8 135, ICD 9 135) Localized Lupus (ICD 8 695.40, ICD 9 695E) Ankylosing Spondylitis (ICD 8 712.40, ICD 9 720A) Psoriatic Arthritis (ICD 8 696.0, 713D, ICD 9 696A)

Study	Methods	Participants	Interventions	Outcomes
Nyren (1998b)	Retrospective Cohort Study **Study Dates** Breast surgery took place from 1965 to 1993. Follow up from Jan 1972 to Dec 1993 **Group Selection** Exposed: All records in the National Swedish Inpatient register that contained the surgical code for breast augmentation with foreign material. These were divided into 2 subcohorts - those with a diagnosis of breast cancer and those who had received implants for other reasons (mainly cosmetic). Unexposed: All records, of patients who had received breast reduction surgery, were selected from the same source. From these, 1 woman was selected as a control for each subject in the cosmetic implant group. They were matched on age (5 yrs), hospital and calendar year at operation (2 yrs). Group Determination Exposed: Medical records - National Swedish Inpatient Registar Unexposed: same **Ascertainment of Outcome** Exposed: Medical Records - records were reviewed to confirm diagnoses Unexposed: same Blinding: not reported	**Country**: Sweden **Exposed**: N = 7433 **Unexposed**: N = 3353 Mean follow up: exposed cosmetic 10.3 years; exposed reconstruction 6.0 years; unexposed 9.9 years % Reconstruction Due to Breast Cancer: 53 (separate analysis provided) **Response Rate** All eligible records included. Censoring occurred at date of immigration, death or end of follow up.	**Implant Type**Type Unspecified 7%Silicone Gel Filled 56% (no separate analysis) Saline 24% Double Lumen 12% Polyurethane Coated <0.1% **Exposure** Injections Excluded: no mention Rupture Described: no Explantation Described: no Duration Described: yes	**Diagnoses** Multiple Sclerosis (ICD-7 345.00, ICD-8 340.99, ICD-9 340) Neuritis of the Optic Nerve (ICD-7345.10, ICD-8341.01, ICD-9341A) Amyotrophic Lateral Sclerosis (ICD-7356.10, ICD-8 348.00, ICD-9 335C) Diseases of the Nerve Roots and Plexuses (ICD-9 353) Mononeuritis of the Upper Extremity -Lesion of the Median Nerve (ICD-7 368.01, ICD-8 357.01, ICD-9354B) -Lesion of the Ulnar Nerve (ICD-7 368.00, ICD-8 357.00, ICD-9 354C) -Lesion of the Radial Nerve (ICD-7 368.02, ICD-8 354.01, ICD-9 354D) Mononeuritis of the Lower Extremity (ICD-9 355) Guillian-Barre Syndrome (ICD-7 364.20, ICD-8 354.01, ICD-9 357A) Meniere's Disease (ICD-7 395, ICD-8 385, ICD-9 368A)

Study	Methods	Participants	Interventions	Outcomes
Park (1998)	**Retrospective Cohort Study** **Study Dates** Implantation took place from 1982-1991. No other dates reported. **Group Selection** Exposed: 1)Augmentation Group - All women in SE Scotland who had received silicone gel implants for reasons other than reconstruction following mastectomy, between 1982 and 1991 were approached to participate. 2) Reconstruction Group - All women from the same region who had undergone reconstruction with silicone gel implants following mastectomy for breast cancer. Patients who had locally advanced or metabolic disease at the time of initial diagnoses were excluded. Only those patients who had survived 1 year following their operations were eligible. Unexposed: 1) Augmentation Control Group (a) Examination controls - Women attending the plastic surgery out patient department who were of similar age as augmentation group. 2) Augmentation Control Group (b) Blood Sample Controls - Women of similar age as augmentation group recruited anonymously from local maternity unit. 3) Reconstruction Controls - Patients from the data base of the Breast Unit were matched to reconstruction patients on age (6 months), stage of disease at diagnosis and time of operation (3 months). **Group Determination** Exposed: medical records – operating books Unexposed: medical records Ascertainment of Outcome: Exposed: Direct measurement (medical exam and serological analysis), medical	**Country**: Scotland **Exposed**: Augmentation Group N = 110, Reconstruction Group N = 207 **Unexposed**: Augmentation - Examination Controls N = 128, Blood Controls N = 203, Reconstruction Controls N = 88 Mean Age: Exposed: Augmentation Group 34.1years, Reconstruction Group 55.2 years, Unexposed: Augmentation (a) Examination Controls 33.6 years, (b) Blood Controls 31.2 years, Reconstruction Controls 55.8 years Mean Years Since Implantation: Augmentation Group 5.9 Reconstruction Group 5.3 Reconstruction Due to Breast Cancer: 64% (separate analysis) Cosmetic: 36% Bilateral: 77% Unilateral: 32% **Response Rate** Augmentation Group 59% Augmentation controls (both groups) not reported Reconstruction Group72% Reconstruction controls 50%	**Implant Type** Silicone gel filled (average size 258 ml) **Exposure** Rupture Described: yes Explantation Described: yes Duration Described: yes Excluded Injections yes	**Diagnosis** Rheumatoid Arthritis (ACR criteria) **Lab Values** Positive ANA (human cell culture, titre <40 considered normal) **Symptoms** joint pain muscle pain fatigue Raynaud's phenomenon dysphagia weight loss constipation, psychiatric photosensitivity rash edema lymphadenopathy sclerodactyly abnormal pigment telangectasia

	records, and self report (medical history and quality of life questionnaire) Unexposed: same **Blinding** Not reported

Study	Methods	Participants	Interventions	Outcomes
Sanchez (1995)	**Retrospective Cohort Study** **Study Dates** 1976 - rheumatic conditions which occurred since this date were enumerated 1990 - Implantation must have taken place prior to this date. 1992- Information regarding exposure was collected via mailed questionnaires. 1980-1992 - Information regarding rheumatic conditions was collected via mailed questionnaires (biannually). 1992 - Participants who had completed the 1992 biannual questionnaire and had reported rheumatic disease prior to June 1 1990 were sent a screening questionnaire regarding CTD. **Group Selection** Participants in Nurses Health Study assembled in June 1976 – married female RNs age 30-55 residing in 11 US states. Exposed: women reporting any breast implants or injections on questionnaire (surgery prior to 1990) Unexposed: reporting no implants or injections on questionnaire **Group Determination** Exposed: self report (mailed questionnaire). Self report validated in a random sample by blinded physician medical record review. Unexposed: self report (mailed questionnaire) Ascertainment of Outcome: Exposed: self report (questionnaire), medical records - Women who had reported CTD were then sent a screening questionnaire including 30 criteria based symptoms (sensitivity 83 -96%, specificity 83-93%) for detecting RA, SLE, SSc, Sjogren's,	**Country**: United States **Exposed**: N = 1183 **Unexposed**: N = 86318 SES: All nurses Caucasian: 95% (whole cohort) Reconstruction Due to Breast cancer: 33% (no separate analysis) Bilateral: 79% Exposed subjects with 2+ operations: 23% Mean years since implantation: 9.9 (+/- 6.4) Cohort with breast implants: 1.4% **Response Rate** Whole cohort: 1976 baseline questionnaire 70%, 1992 biennial questionnaire 81%, Supplementary questionnaire to those who reported breast implants in 1992 - 97.2%, Screening questionnaire to those who had reported disease 90%	**Implant Type** Unspecified: 5% Silicone gel filled: 74% (analysed separately) Saline: 14% Double lumen: 6% Polyurethane coated: 1% **Exposure** Rupture described: no Explantation described:no Duration described: yes Excluded Injections: yes	**Diagnosis** Rheumatoid Arthritis (ACR criteria) Scleroderma (ACR criteria) Sjogren's Syndrome (Fox et al criteria) Polymyositis / Dermatomyocitis (Bohan and Peter criteria) Systemic Lupus Erythematosus (ACR criteria) Mixed Connective Tissue Disease (Alarcon, Sigovis and Cardiel criteria) Definite CTD (combined endpoint comprised of all the above) Self Reported Connective Tissue Disease (women with possible early, milder or atypical forms of CTD who did not meet the standard classification criteria) **Symptoms** Self Reported Signs or Symptoms of CTD Documented Signs or Symptoms of CTD

	Inflammatory Myositis, and Mixed Connective Tissue Disease. Those who had a positive questionnaire (at least 2 swollen joints for >6 weeks or 3 positive answers) had their medical records reviewed by 2 rheumatologists. Date of onset was defined as date of diagnosis in chart. Less stringent criteria were used for a separate analysis - patients who reported rheumatic disease on any biennial questionnaire, patients who had a positive screening questionnaire, or patients who had any 1 of 41 signs, symptoms or laboratory features on the medical record abstraction form were included. Unexposed: same **Blinding** Data regarding implant history was entered by blinded researchers. Medical records regarding outcome were reviewed by blinded physicians.	

Study	Methods	Participants	Interventions	Outcomes
Strom (1994)	**Case Control Study** **Study Dates** 1985-1987 - Cases and controls identified for a general risk factor study not involving implants. June 1992 - Sept 1992 Subjects were contacted again to be interviewed regarding breast implantation prior to the index date of the previous study. **Group Selection** Case Definition: Outpatients with a new (incident) or recent (within 3 years) clinical diagnosis of SLE or lupus-like illness were identified from Philadelphia rheumatology practices (73%) and local Lupus Foundation (27%). Cases without matched controls were excluded Control Definition: Internal Controls - Friends of cases, matched on sex and age (5 years) were randomly selected from alphabetical order and random number table. External Controls - Population based controls from the Cancer and Steroid Hormone study which studied events diagnosed from 1980 - 1982. **Group Determination** Cases: medical records (not specified) Controls (internal): self report (not specified) - excluded those with SLE **Ascertainment of Exposure** Cases: self report (telephone interview) Controls (internal): same **Blinding** not reported	**Country**: Philadelphia, USA **Cases**: N = 133 **Controls**: Internal Controls N = 100, External Controls N = 4754 Years since implantation: cases: 8 years (only 1 case) Cases with breast implants: 0.75% Controls with breast implants: internal controls 0, external controls 0.17 **Response Rate** Cases: Original Study - 89% Implant Study - cases 75.9% of original subjects Controls: Original Study - 85.1%Implant Study - 77.6% of original subjects	**Implant Type** Unspecified **Exposure** Rupture described: no Explantation described: no Duration described: yes Excluded injections: no (external controls)	**Diagnosis** Scleroderma (4 or more revised ARA criteria)

Study	Methods	Participants	Interventions	Outcomes
Teel (1997)	Case Control Study **Study Dates** Cases diagnosed between Jan 1983 and Dec 1991. "Pre existing control group" interviewed between 1986 and 1991. "New" control group selected from 1994 – 1996. **Group Selection** Case Definition Female residents of King's County diagnosed by a rheumatologist as having one of five connective tissue diseases. Control Definition "Pre existing" controls had been identified through random digit dialing for previous epidemiologic studies. "New" controls were selected by random digit dialing and matched to cases on age and year of diagnosis. All controls were residents of King County at their reference dates. Those with a history of CTD prior to reference date were excluded. **Group Determination** Cases: Medical records were reviewed by trained research assistants. Cases were classified as definite (case met all diagnostic criteria and had been diagnosed by rheumatologist) or probable (rheumatologist made diagnosis but case fell one feature short of requisite criteria or criteria were met but rheumatologist had labeled the disease as probable). 96% of probable cases were re-abstracted to confirm eligibility Controls: "Pre existing" controls - self report (not clear if interview or questionnare). "New" controls – self report - mailed questionnaire (non respondents administered same	**Country**: Washington State, USA **Cases**: N = 427 **Controls**: "Pre-existing" N = 1688; "New" N = 1577 Mean age at reference date: cases 45.2 years; "pre-existing" controls 48.1 years; "new" controls 41.7 years Race – Caucasian: cases 79.9%; "pre existing" controls 89.1 %; "new" controls 93.7% Body Mass Index: cases 23.2; "pre-existing" controls 23.5; "new" controls 23.2 Ever Married: cases 83.1%; "pre existing" controls 91.0 %; "new" controls 81.4% Education: cases 13.9 years; "pre existing" controls 13.9 years; "new" controls 14.1 years Breast Cancer: : cases 1.6%; "pre existing" controls 2.3 %; "new" controls 1.3% Cases with breast implants: 1.4% Controls with breast implants: "pre existing" 1.0%; "new" 1.1% **Response Rate** Cases: 80.3% Controls: "pre existing" controls 79.0%; "new controls" 79.0%	**Implant Type** Unspecified: N = 5 (1 case, 4 controls) Silicone Gel-Filled: N = 32 (4 cases, 28 controls) Saline: N = 8 (1 case, 7 controls) Separate analysis for Silicone Gel-Filled implants: no **Exposure** Rupture described: no Explantation described: no Duration described: no Injections excluded: not reported	**Diagnoses** Systemic Lupus Erythematosus (ACR criteria) Systemic Sclerosis/Crest (ACR criteria) Sjogren's Syndrome (ACR criteria) Polymyositis (Bohan criteria) Mixed Connective Tissue Disease (Sharp criteria) Any Connective Tissue Disease (all cases combined)

questionnaire by phone)

Ascertainment of Exposure
Cases: Self report - mailed questionnaire (non respondents administered same questionnaire by phone).
Controls: "Pre existing" controls – self report – interview. "New" controls same as for cases.

Blinding
Not reported.

Study	Methods	Participants	Interventions	Outcomes
Wells (1994)	**Retrospective Cohort Study** **Study Dates** 1970-1990 - dates of implantation Oct 13 1990 - Questionnaire regarding symptoms was mailed to both exposed and unexposed plastic surgery patients. July 11 1991 - Second questionnaire was mailed to non responders. (In addition, a telephone follow up for which no dates were reported, was conducted with a random sample of non responding women.) **Group Selection** Subjects age 20 - 60 who had not undergone silicone chin or nose implant or collagen injections selected from a single plastic surgery practice. Exposed: women who had "silicone breast implants" for aesthetic or reconstructive purposes. Unexposed: Women who had a cosmetic procedure (blepharoplasty, rhinoplasty or liposuction) other than breast implants. Those who subsequently obtained breast implants were excluded. **Group Determination** Exposed: medical records Unexposed: same **Ascertainment of Outcome** Exposed: self report - mailed questionnaire and for a random sample of non responders (n=8) telephone survey Unexposed: same (telephone survey n-19) **Blinding** not reported	**Country**: Florida, USA **Exposed**: N = 222 **Unexposed**: N = 80 Median age: exposed 37(+/- 0.67), unexposed 46.5 (+/-1.63) Caucasian: 98% (of all subjects) Median year of operation: exposed 1986 (+/-0.48), unexposed 1988 (+/-0.31). 8% of implant group had surgery >10 years ago. None of controls had surgery > than 7 years previously. Good health before surgery: exposed 98%, unexposed 100% Prevalence of allergies: exposed 38%, unexposed 32% History of breast cancer: 0 in cohort **Response Rate** Exposed: 59% Unexposed: 46%	**Implant Type** Silicone gel filled (assume - article states "silicone breast implants" **Exposure** Rupture described: no Explantation described: no Duration described: yes Excluded Injections: yes	**Diagnosis** Systemic sclerosis Raynaud's phenomenon Arthritis (not defined whether RA or not) Note: study looked at self reported diagnoses only, no criteria reported. **Symptoms** easily tired muscle pain swollen glands neck tender glands neck swollen glands under arm tender glands under arm rashes skin thickening skin tightness change in skin colour hair loss arms and legs persistent fever change in hand colour with cold breathing difficulty weight loss > 10 lbs. weight gain > 10 lbs. swollen joints painful joints general stiffness Note: patients were asked if they experienced these outcomes either before or after surgery. Only those symptoms reported as being post surgical which were not present before hand were analysed.

Study	Methods	Participants	Interventions	Outcomes
Winther (1998)	Retrospective Cohort Study: Study Dates: Breast surgery took place between 1977- 1992. Follow up to Dec 31 1993 **Group Selection** Exposed: Women identified through Danish Central National Register of Patients (NRP) who had received implants at public hospitals between for cosmetic reasons. Unexposed: Women from the same source who had undergone breast reduction surgery. **Group Determination** Exposed: NRP records (ICD-8 38500, 38540) Unexposed: NRP records (ICD-8 38400,38460) **Ascertainment of Outcome** Exposed: NRP records. Hospital medical records were reviewed to validate neurologic diagnoses obtained form NRP Unexposed: NRP records. Hospital medical records were reviewed to validate neurologic diagnoses for which an increased occurrence was observed in the exposed cohort **Blinding** Medical records reviewed by blinded neurologist	**Country**: Denmark **Exposed**: N = 1335 **Unexposed**: N = 7071 Median Age at Entry: Exposed 31; Unexposed 31 Median Length of Follow up: Exposed 8.5 yrs; Unexposed 7.7 yrs **Response Rate** All eligible records included. Follow up continued to Dec 31 1993, death or date of last health care visit.	**Implant Type** Silicone breast implants **Exposure** Injections Excluded: yes Rupture Described: no Explantation Described: no Duration Described: yes	**Diagnoses** (All cases represented neurologic disease requiring hospitalization and were classified according to ICD 8) Multiple Sclerosis (ICD 340, Poser criteria) Other Demyelinating CNS Neuropathies (ICD 341) Motor Neuropathy (ICD 348, includes ALS) Peripheral Neuropathies -Brachial Neuropathy (ICD 352) Sciatic Neuropathy (ICD 353.99) Polyneuropathy (ICD 354, includes Guillian Barre) Neuropathy,NOS (ICD 355.09) Other Peripheral Neuropathies (ICD 357.99) Optical Retino - and Neuropathy (ICD 367) Meniere's Disease (ICD 385.99) Myasthenia Gravis (ICD 733.09)

Study	Methods	Participants	Interventions	Outcomes
Wolfe (1995)	**Case Control Study** **Study Dates** not reported Case Definition: patients with fibromyalgia, patients with rheumatoid arthritis Control Definiton: Two groups - 1) patients with osteoarthritis, 2) women randomly selected from the general population **Group Determination** not reported **Ascertainment of Exposure** Cases: self report - mailed questionnaires Controls: Osteoarthritis controls - self report - mailed questionnaires, community controls - self report – telephone interview **Blinding** not reported	**Country**: Kansas, USA **Cases**: Fibromyalgia (FM) N = 533, Rheumatoid Arthritis (RA) N = 637 **Controls**: Osteoarthritis (OA) N = 477, Community N = 655 Mean age at interview:cases: RA 64.4 years, FM 51.6 years controls: OA 67.4 years, community 55.3 years Mean age at disease onset: Cases: RA 47.1 years, FM 38.5 years Controls: OA 52.7 years Cases with implants: Fibromyalgia 1.31%, Rheumatoid Arthritis 0.47% Controls with implants: Community controls 0.31%. Osteoarthritis controls 0.42 **Response Rate** not reported	**Implant Type** Unspecified (referred to as silicone breast implants but not specific about the filling) **Exposure** Rupture described: no Explantation described: no Duration described: no Excluded injections: not reported	**Diagnosis** Rheumatoid Arthritis (criteria not reported) Fibromyalgia (criteria not reported)

APPENDIX A
SEARCH STRATEGY

APPENDIX A
SEARCH STRATEGY

Set Search 1

---

001 breast implants/
002 (breast adj3 implant$).tw.
003 (breast adj3 (augmentation or reconstruction)).tw.
004 (breast adj3 prosthes#s).tw.
005 or/1-3
006 breast/ or breast$.tw.
007 implants, artificial/
008 prosthesis/
009 exp silicones/ or silicone$.tw.
010 or/7-9
011 (5 or 6) and 10
012 mammaplasty/ or mammaplasty.tw.
013 surgery, plastic/
014 breast/su
015 or/12-14
016 (augment$ or implast$).tw.
017 (reconstruct$ or cosmetic or prosthes#s).tw.
018 15 and (16 or 17)
019 5 or 11 or 18
020 exp arthritis, rheumatoid/
021 (felty$ adj2 syndrome).tw.
022 (caplan$ adj2 syndrome).tw.
023 rheumatoid nodule.tw.
024 (sjogren$ adj2 syndrome).tw.
025 (sicca adj2 syndrome).tw.
026 still$ disease.tw.
027 (spondylitis adj2 ankylosing).tw.
028 bechterew$ disease.tw.
029 (arthritis adj2 rheumat$).tw.
030 or/20-29
031 19 and 30
032 scleroderma, circumscribed/
033 ((scleroderma adj localized) or progressive or diffuse or sy
034 exp scleroderma, systemic/
035 ((crest or crst) adj syndrome).tw.
036 morphea.ti,ab,sh. or dermatosclerosis.tw.
037 sclerodacty$.tw.
038 exp calcinosis/ or calcinosis.tw.
039 exp esophageal motility disorders/
040 esophag$.tw.

041 ataxia telangiectasia/
042 telangiectasia, hereditary hemorrhagic/
043 telangiectasia.tw.
044 osler-rendu.tw.
045 louis-bar.tw.
046 raynaud's disease/ or raynaud$.tw.
047 or/32-46
048 19 and 47
049 48

Set Search 2

---

001 breast implants/
002 (breast adj3 implant$).tw.
003 (breast adj3 (augmentation or reconstruction)).tw.
004 (breast adj3 prosthes#s).tw.
005 or/1-3
006 breast/ or breast$.tw.
007 implants, artificial/
008 prosthesis/
009 exp silicones/ or silicone$.tw.
010 or/7-9
011 (5 or 6) and 10
012 mammaplasty/ or mammaplasty.tw.
013 surgery, plastic/
014 breast/su
015 or/12-14
016 (augment$ or implast$).tw.
017 (reconstruct$ or cosmetic or prosthes#s).tw.
018 15 and (16 or 17)
019 5 or 11 or 18
020 exp lupus erythematosus, systemic/
021 (lupus adj (nephritis or erythematosus or disseminatus)).tw.
022 libman-sacks.tw.
023 antiphospholipid syndrome/
024 antiphospholipid.tw.
025 or/20-24
026 19 and 25
027 dermatomyositis/ or dermatomyositis.tw.
028 19 and 27
029 polymyositis/
030 myositis.ti,ab,sh. or polymyositis.tw.
031 20 or 30
032 19 and 31
033 arthritis, psoriatic/

034 (psoriatic adj2 (arthrit$ or arthropathica)).tw.
035 33 or 24
036 19 and 35
037 28

Set Search 3

---

001 breast implants/
002 (breast adj3 implant$).tw.
003 (breast adj3 (augmentation or reconstruction)).tw.
004 (breast adj3 prosthes#s).tw.
005 or/1-3
006 breast/ or breast$.tw.
007 implants, artificial/
008 prosthesis/
009 exp silicones/ or silicone$.tw.
010 or/7-9
011 (5 or 6) and 10
012 mammaplasty/ or mammaplasty.tw.
013 surgery, plastic/
014 breast/su
015 or/12-14
016 (augment$ or implast$).tw.
017 (reconstruct$ or cosmetic or prosthes#s).tw.
018 15 and (16 or 17)
019 5 or 11 or 18
020 exp vasculitis/
021 angiitis.tw.
022 vasculitis, allergic cutaneous/
023 vasculitis.tw,sh.
024 arteritis.tw.
025 (thrombophlebitis or phlebitis).tw.
026 thromboangiitis.tw.
027 (behcet$ or churg-strauss).tw.
028 wegener$.tw.
029 mucocutaneous lymph.tw.
030 or/20-29
031 19 and 30
032 exp inflammatory bowel diseases/
033 ulcerative colitis.tw.
034 crohn$.tw.
035 (colitis or ileitis or enteritis).tw.
036 (rectocolitis or proctocolitis).tw.
037 inflammatory bowel.tw.

038 or/32-37
039 19 and 38
040 polychondritis, relapsing/
041 polychondritis.tw.
042 40 or 41
043 19 and 42
044 fibromyalgia/
045 (fibromyalgia or fibrositis).tw.
046 muscular rheumatism.tw.
047 fatigue syndrome, chronic/
048 chronic fatigue.tw.
049 myalg$.tw.
050 encephalomyelitis.tw.
051 encephalomyelitis.tw.
052 or/44-51
053 19 and 52
054 53

Set Search 4

---

001 breast implants/
002 (breast adj3 implant$).tw.
003 (breast adj3 (augmentation or reconstruction)).tw.
004 (breast adj3 prosthes#s).tw.
005 or/1-3
006 breast/ or breast$.tw.
007 implants, artificial/
008 prosthesis/
009 exp silicones/ or silicone$.tw.
010 or/7-9
011 (5 or 6) and 10
012 mammaplasty/ or mammaplasty.tw.
013 surgery, plastic/
014 breast/su
015 or/12-14
016 (augment$ or implast$).tw.
017 (reconstruct$ or cosmetic or prosthes#s).tw.
018 15 and (16 or 17)
019 5 or 11 or 18
020 connective tissue diseases/
021 exp cartilage diseases/
022 cellulitis/
023 exp collagen diseases/
024 cutis laxa/
025 dupuytren's contracture/

026 homocystinuria/
027 marfan syndrome/
028 mixed connective tissue disease/
029 exp mucinoses/
030 neoplasms, connective tissue/
031 noonan syndrome/
032 osteopoikilosis/
033 exp panniculitis/
034 pseudoxanthoma elasticum/
035 mctd.tw.
036 sharp syndrome.tw.
037 human adjuvant.tw.
038 mixed connective tissue.tw.
039 sclerosis-like.tw.
040 fibrous banding.tw.
041 skin thickening.tw.
042 arthralgia/
043 (arthralgia or polyarthralgia).tw.
044 or/20-43
045 19 and 44
046 scleroderma, circumscribed/
047 ((scleroderma adj localized) or progressive or diffuse or sy
048 exp scleroderma, systemic/
049 ((crest or crst) adj syndrome).tw.
050 morphea.ti,ab,sh. or dermatosclerosis.tw.
051 sclerodacty$.tw.
052 exp calcinosis/ or calcinosis.tw.
053 exp esophageal motility disorders/
054 esophag$.tw.
055 ataxia telangiectasia/
056 telangiectasia, hereditary hemorrhagic/
057 telangiectasia.tw.
058 osler-rendu.tw.
059 louis-bar.tw.
060 raynaud's disease/ or raynaud$.tw.
061 or/46-60
062 19 and 61
063 45 not 62
064 63

Set Search 5

---

001 breast implants/
002 breast adj3 implant$).tw.
003 (breast adj3 (augmentation or reconstructio

004 (breast adj3 prosthes#s).tw.
005 or/1-3
006 breast/ or breast$.tw.
007 implants, artificial/
008 prosthesis/
009 exp silicones/ or silicone$.tw.
010 or/7-9
011 (5 or 6) and 10
012 mammaplasty/ or mammaplasty.tw.
013 surgery, plastic/
014 breast/su
015 or/12-14
016 (augment$ or implast$).tw.
017 (reconstruct$ or cosmetic or prosthes#s).tw
018 15 and (16 or 17)
019 5 or 11 or 18
020 randomized controlled trial.pt.
021 controlled clinical trial.pt.
022 controlled clinical trials/
023 exp cross-sectional studies/
024 cross-sectional.tw.
025 prospective.tw.
026 retrospective.tw.
027 exp cohort studies/
028 exp case-control studies/
029 or/20-28
030 19 and 29
031 control$.tw.
032 19 and 31
033 30 or 32
034 limit 33 to human
035 exp arthritis, rheumatoid/
036 exp calcinosis/
037 exp scleroderma, systemic/
038 exp esophageal motility disorders/
039 exp lupus erythematosus, systemic/
040 arthritis, psoriatic/
041 vasculitis.tw.
042 exp inflammatory bowel diseases/
043 fibromyalgia/
044 fatigue syndrome, chronic/
045 connective tissue diseases/
046 mixed connective tissue disease/
047 exp collagen diseases/
048 exp cartilage diseases/

049 neoplasms, connective tissue/
050 exp Mucinoses/
051 cellulitis/
052 scleroderma.tw.
053 antiphospholipid syndrome/
054 polymyositis/
055 arteritis.tw.
056 (colitis or ileitis).ti,ab,rw,sh. or enteri
057 exp panniculitis/
058 arthralgia/
059 telangiectasia.tw.
060 raynaud's disease/ or raynaud$.tw.
061 or/35-50
062 34 not 61
063 2 or 3 or 4 or 6 or 12 or 14
064 63 and 9
065 1 or 64
066 breast implantation/
067 65 or 66
068 29 and 67
069 31 and 67
071 limit 71 to human

Toxline Search

001 (breast implant$ or breast) and silicone$
002 exclude medline

Dissertation Abstracts

001 breast implant
002 breast implants
003 breast and silicone

APPENDIX B
DATA EXTRACTION FORMS

SILICONE BREAST IMPLANTS AND CONNECTIVE TISSUE DISEASE
CASE CONTROL STUDY

Identification	Article # Review # Reviewer
Title	
Investigator	Year
Setting	Location Language Study Name
Dates of Enrolment	
Diagnoses	❑ SSc ❑ ACR ❑ Morphea ❑ ACR ❑ RA ❑ ACR ❑ SLE ❑ ACR ❑ FM ❑ ACR ❑ Sjogrens ❑ ACR ❑ Dermatomyositis ❑ ACR ❑ Polymyositis ❑ ACR ❑ Vasculitis ❑ ACR ❑ Ankylosing Spondylitis ❑ Psoriatic Arthritis ❑ Arthritis Associated With Inflammatory Bowel Disease ❑ Polychondritis ❑ Mixed Connective Tissue Disease ❑ Raynaud's Phenomenon ❑ Any Connective Tissue Disease (Combined Endpoint) ❑ Other _____ ❑ Other _____
Implant	❑ Implant Type Unspecified ❑ Injection - Silicone ❑ Silicone Gel Filled ❑ Injection - Collagen ❑ Saline ❑ Double lumen ❑ Polyurethane coated

Comments: _____

_____

_____

Methodology

	Cases	Control
# Identified		
# Excluded		
Group N		
Group Selection	Case Definition Excluded cases with Dx prior to implants? ❑ Y ❑ N ❑ NA	Control Definition ❑ Randomly Selected ❑ Excluded Hist of Disease ❑ Community Controls ❑ Hospital Controls ❑ Matched _____ ❑ Unmatched ❑ Single Control ❑ Multiple Controls_____
Group Determination	❑ Direct Measurement ❑ Medical Records ❑ Self Report	❑ Direct Measurement ❑ Medical Records ❑ Self Report
Ascertainment of Exposure	❑ Direct Measurement ❑ Medical Records ❑ Self Report Blinding ❑ Y ❑ N	❑ Direct Measurement ❑ Medical Records ❑ Self Report Blinding ❑ Y ❑ N
Exposure	Rupture Described ❑ Y ❑ N Explantation Described ❑ Y ❑ N Duration Described ❑ Y ❑ N Excluded Injections ❑ Y ❑ N	

Subject Characteristics

Characteristic	Cases	Controls
$\bar{x}$ Age		
SES (Define)		
% Family History of Disease		
% Caucasian		
% Rupture		
% Explantation		
$\bar{x}$ Yrs Since Implantation		
% Reconstruction Due to Breast Cancer		
% Cosmetic		
% Bilateral		
% Unilateral		

Group Differences:

_____
_____

_____
_____

_____
_____

_____
_____

Data Analysis: ❑ All subjects ❑ Excludes ascertainment exposure unknown

Exposure	**N**			**Crude OR (CI)**	**Adjusted OR (CI)**	**Factors Adjusted**	**Translation**
		Case	Control			❑ Age ❑ Education ❑ Income ❑ Marital Status ❑ Race ❑ ____________ ❑ ____________ ❑ ____________	
	E						
	E						
	T						
		Case	Control			❑ Age ❑ Education ❑ Income ❑ Marital Status ❑ Race ❑ ____________ ❑ ____________ ❑ ____________	
	E						
	E						
	T						
		Case	Control			❑ Age ❑ Education ❑ Income ❑ Marital Status ❑ Race ❑ ____________ ❑ ____________ ❑ ____________	
	E						
	E						
	T						

SILICONE BREAST IMPLANTS AND CONNECTIVE TISSUE DISEASE COHORT STUDY

Identification	Article # Review # Reviewer
Title	
Investigator	Year
Setting	Location Language Study Name
Dates of Enrolment	
Diagnoses	❑ SSc ❑ ACR ❑ Morphea ❑ ACR ❑ RA ❑ ACR ❑ SLE ❑ ACR ❑ FM ❑ ACR ❑ Sjogrens ❑ ACR ❑ Dermatomyositis ❑ ACR ❑ Polymyositis ❑ ACR ❑ Vasculitis ❑ ACR ❑ Ankylosing Spondylitis ❑ Psoriatic Arthritis ❑ Arthritis Associated With Inflammatory Bowel Disease ❑ Polychondritis ❑ Mixed Connective Tissue Disease ❑ Raynaud's Phenomenon ❑ Any Connective Tissue Disease (Combined Endpoint) ❑ Other _____ ❑ Other _____
Implant	❑ Implant Type Unspecified ❑ Injection - Silicone ❑ Silicone Gel Filled ❑ Injection - Collagen ❑ Saline ❑ Double lumen ❑ Polyurethane coated

Comments: _____

_____

_____

Methodology

Design: ❑ Prospective Cohort ❑ Retrospective Cohort
❑ Internal Cohort ❑ External Cohort

	Exposed (Cohort)	Unexposed
# Identified (Describe)		
# Excluded (Describe)		
Group N		
All S's Accounted ?		
Group Selection	Exposure: Injections Excluded ❑ Y ❑ N Rupture Described ❑ Y ❑ N Explantation Desc. ❑ Y ❑ N Duration Described ❑ Y ❑ N	
Group Determination	❑ Direct Measurement ❑ Medical Records ❑ Self Report Blinding ❑ Yes ❑ No	❑ Direct Measurement ❑ Medical Records ❑ Self Report Blinding ❑ Yes ❑ No
Ascertainment of Outcome	❑ Direct Measurement ❑ Medical Records ❑ Self Report Blinding ❑ Yes ❑ No	❑ Direct Measurement ❑ Medical Records ❑ Self Report Blinding ❑ Yes ❑ No
Outcome		

Subject Characteristics

Characteristic	Cohort	Exposed	Unexposed
$\bar{x}$ Age			
SES (Define)			
% Family History of Disease			
% Caucasion			
% Rupture			
% Explantation			
$\bar{x}$ Yrs Since Implantation			
% Reconstruction Due to Breast Cancer			
% Cosmetic			
% Bilateral			
% Unilateral			

Group Differences:

_____

_____

_____

_____

Data Analysis: ❑ All subjects ❑ Loss to follow up excluded

Outcome and Exposure	N				Crude OR/RR (CI)	Adjusted OR/RR (CI)	Factors Adjusted	Translation
Outcome		D	D	T/PY			❑ Age ❑ Education ❑ Income ❑ Marital Status ❑ Race ❑ ________ ❑ ________ ❑ ________	
	E							
Exposure	E							
	T							
Outcome		D	D	T/PY			❑ Age ❑ Education ❑ Income ❑ Marital Status ❑ Race ❑ ________ ❑ ________ ❑ ________	
	E							
Exposure	E							
	T							
Outcome		D	D	T/PY			❑ Age ❑ Education ❑ Income ❑ Marital Status ❑ Race ❑ ________ ❑ ________ ❑ ________	
	E							
Exposure	E							
	T							

INDEX